STN - Registry | Caplus

L1 STRUCTURE UPLOADED

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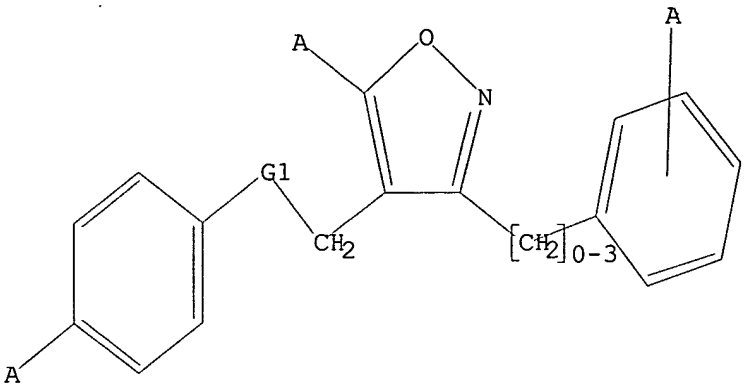
L1 HAS NO ANSWERS
L1 STR



G1 O,N

Structure attributes must be viewed using STN Express query preparation.

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FULL SEARCH INITIATED 12:54:09 FILE 'REGISTRY'
FULL SCREEN SEARCH COMPLETED - 4398 TO ITERATE

100.0% PROCESSED 4398 ITERATIONS 138 ANSWERS
SEARCH TIME: 00.00.01

L2 138 SEA SSS FUL L1

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COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	172.10	172.31

FILE 'CAPLUS' ENTERED AT 12:54:17 ON 27 FEB 2007
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FILE LAST UPDATED: 26 Feb 2007 (20070226/ED)

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L3 48 L2

=> d ibib abs hitstr 1-48

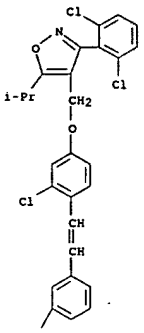
L3 ANSWER 1 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1348484 CAPLUS
DOCUMENT NUMBER: 146:93196
TITLE: Farnesoid X receptor agonist reduces serum asym. dimethylarginine levels through hepatic dimethylarginine dimethylaminohydrolase-1 gene regulation
AUTHOR(S): Hu, Tonghuan; Chouinard, Michael; Cox, Amy L.; Sipes, Philip; Marcelo, Marialuisa; Ficorilli, James; Li, Shuyu; Gao, Hong; Ryan, Timothy P.; Michael, M. Dodson; Michael, Laura F.
CORPORATE SOURCE: Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Journal of Biological Chemistry (2006), 281(52), 39831-39838
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The farnesoid X receptor (FXR, NR1H4) is a bile acid-responsive nuclear receptor that plays critical roles in the transcriptional regulation genes involved in cholesterol, bile acid, triglyceride, and carbohydrate metabolism By microarray anal. of hepatic genes from female Zucker diabetic fatty (ZDF) rats treated with the FXR agonist GW4064, we have identified dimethylarginine dimethylaminohydrolase-1 (DDAH1) as an FXR target gene. DDAH1 is a key catabolic enzyme of asym. dimethylarginine (ADMA), a major endogenous nitric-oxide synthase inhibitor. Sequence anal. of the DDAH1 gene reveals the presence of an FXR response element (FXRE) located 90 kb downstream of the transcription initiation site and within the first intron. Functional anal. of the putative FXRE demonstrated GW4064 dose-dependent transcriptional activation from the element, and we have demonstrated that the FXRE sequence binds the FXR-RXR heterodimer. In vivo administration of GW4064 to female ZDF rats promoted a dose-dependent and >6-fold increase in hepatic DDAH1 gene expression. The level of serum ADMA was reduced concomitantly. These findings provide a mechanism by which FXR may increase endothelium-derived nitric oxide levels through modulation of serum ADMA levels via direct regulation of hepatic DDAH1 gene expression. Thus, beneficial clin. outcomes of FXR agonist therapy may include prevention of atherosclerosis and improvement of the metabolic syndrome.

IT 278779-30-9, GW4064
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(farnesoid X receptor agonist reduces serum asym. dimethylarginine levels through hepatic dimethylarginine dimethylaminohydrolase-1 gene regulation)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 1 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 52 THERE ARE 52 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 2 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:1256610 CAPLUS
DOCUMENT NUMBER: 146:32402
TITLE: Reduction of hair growth using a farnesoid X receptor agonist
INVENTOR(S): Hwang, Cheng Shine
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 8pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2006269496	A1	20061130	US 2005-141798	20050531
WO 2006130330	A2	20061207	WO 2006-US18663	20060515

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

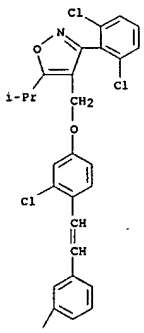
PRIORITY APPLN. INFO.: US 2005-141798 A1 20050531

AB Unwanted mammalian hair growth, preferably human hair growth, such as an androgen stimulated hair growth, is reduced by applying an agonist of farnesoid X receptor, e.g., a bile acid, farnesol, farnesal, etc., in a topical composition at a concentration of 0.1 to 30%. An agonist of farnesoid X receptor is applied to the skin in an amount of 10 to 3000 μg/cm2 of skin in conjunction with shaving. For example, 5% chenodeoxycholic acid in 90% ethanol/10% propylene glycol reduced hamster hair growth by 76.4%.

IT 278779-30-9
RL: COS (Cosmetic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(reduction of hair growth using farnesoid X receptor agonist)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 2 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



PAGE 2-A

L3 ANSWER 3 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2006:610668 CAPLUS
DOCUMENT NUMBER: 145:305597
TITLE: Hologram QSAR studies on farnesoid X receptor activators
AUTHOR(S): Honorio, Kathia M.; Garratt, Richard C.; Polikarpov, Igor; Andricopulo, Adriano D.
CORPORATE SOURCE: Laboratorio de Quimica Medicinal e Computacional, Centro de Biotecnologia Molecular Estrutural, Instituto de Fisica de Sao Carlos, Universidade de Sao Paulo, Sao Carlos, 13560-970, Brazil
SOURCE: Letters in Drug Design & Discovery (2006), 3(4), 261-267
CODEN: LDDDAW; ISSN: 1570-1808
PUBLISHER: Bentham Science Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Farnesoid X receptor (FXR) is an attractive drug target due to its role in the regulation of cholesterol and bile acid levels. Hologram quant. structure-activity relationships (HQSAR) were conducted on a series of FXR activators, and the final model obtained was used to predict the potency of 10 test set compds. The predicted values were in good agreement with the exptl. results.

IT 278779-30-9 291521-35-2 291521-36-3 291521-38-5 291521-40-9 291521-42-1 291521-46-5 291521-48-7 291521-49-8 291521-51-2
RL: PAC (Pharmacological activity); PRP (Properties); BIOL (Biological study)
(hologram QSAR studies on farnesoid X receptor activators)

RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 3 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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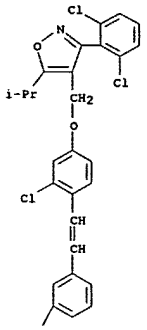

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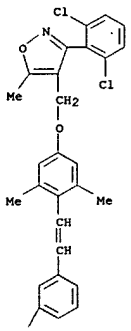
RN 291521-35-2 CAPLUS
CN Benzoic acid, 3-[2-[4-[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]methoxy]-2,6-dimethylphenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 3 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

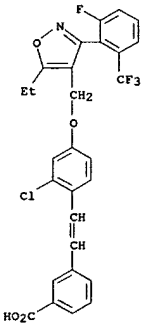
PAGE 1-A



PAGE 2-A

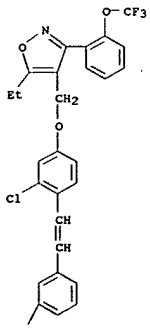
RN 291521-36-3 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[5-ethyl-3-[2-fluoro-6-(trifluoromethyl)phenyl]-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 3 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 291521-38-5 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[5-ethyl-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

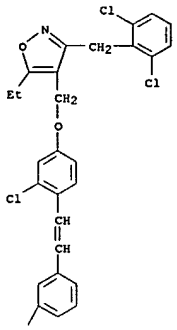


L3 ANSWER 3 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 2-A

RN 291521-40-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-[(2,6-dichlorophenyl)methyl]-5-ethyl-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

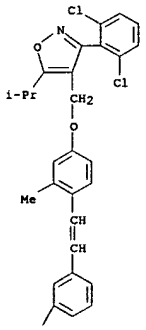


PAGE 2-A

RN 291521-42-1 CAPLUS
CN Benzoic acid, 3-[2-[4-[[3-(2-bromo-6-chlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-chlorophenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 3 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A

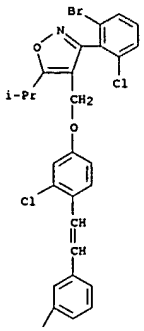


PAGE 2-A

RN 291521-48-7 CAPLUS
CN Benzoic acid, 3-[2-[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2,6-dimethylphenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 3 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A

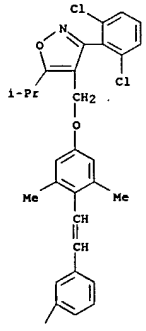


PAGE 2-A

RN 291521-46-5 CAPLUS
CN Benzoic acid, 3-[2-[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 3 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



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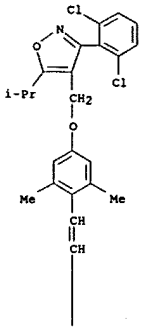
RN 291521-49-8 CAPLUS
CN Benzoic acid, 4-[2-[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2,6-dimethylphenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 3 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



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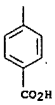
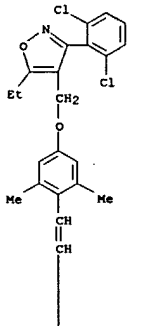


RN 291521-51-2 CAPLUS
CN Benzoic acid, 4-[2-[4-[[3-(2,6-dichlorophenyl)-5-ethyl-4-isoxazolyl]methoxy]-2,6-dimethylphenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 3 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



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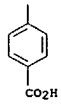

REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS
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L3 ANSWER 4 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

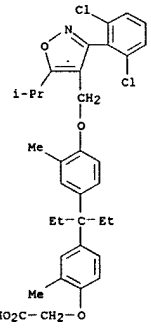
ACCESSION NUMBER: 2006:453901 CAPLUS
DOCUMENT NUMBER: 145:145324
TITLE: Diphenylmethane skeleton as a multi-template for nuclear receptor ligands: Preparation of FXR and PPAR ligands
AUTHOR(S): Kainuma, Masahiko; Kasuga, Jun-ichi; Hosoda, Shinnosuke; Wakabayashi, Ken-Ichi; Tanatani, Aya; Nagasawa, Kazuo; Miyachi, Hiroyuki; Makishima, Makoto; Hashimoto, Yuichi
CORPORATE SOURCE: Institute of Molecular and Cellular Biosciences, University of Tokyo, 1-1-1 Yayoi, Bunkyo-ku, Tokyo, 113-0032, Japan
SOURCE: Bioorganic & Medicinal Chemistry Letters (2006), 16(12), 3213-3218
CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 145:145324

AB Novel, potent farnesoid X receptor (FXR) and peroxisome proliferator-activated receptor α (PPARα) agonists were obtained by using a diphenylmethane skeleton as a substitute for a steroid skeleton.

IT 898253-45-7P 898253-46-8P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of diphenylmethyl ethers as farnesoid X receptor (FXR) and peroxisome proliferator-activated receptor α (PPARα) agonists)

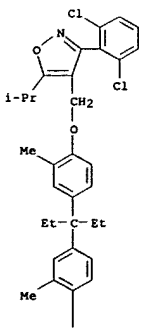
RN 898253-45-7 CAPLUS
CN Acetic acid, [4-[1-[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-3-methylphenyl]-1-ethylpropyl]-2-methylphenoxy]- (9CI)
(CA INDEX NAME)

L3 ANSWER 4 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 898253-46-8 CAPLUS
CN 1,2-Propanediol, 3-[[4-[1-[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-3-methylphenyl]-1-ethylpropyl]-2-methylphenyl]amino]- (9CI) (CA INDEX NAME)

PAGE 1-A



L3 ANSWER 4 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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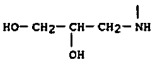
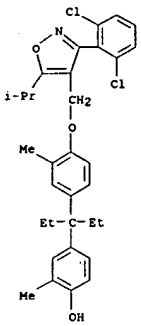
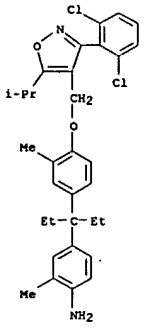


IT 898253-48-0P 898253-49-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of diphenylmethyl ethers as farnesoid X receptor (FXR) and
peroxisome proliferator-activated receptor α (PPARα) agonists)
RN 898253-48-0 CAPLUS
CN Phenol, 4-[1-[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-3-methylphenyl]-1-ethylpropyl]-2-methyl- (9CI) (CA INDEX NAME)



RN 898253-49-1 CAPLUS
CN Benzenamine, 4-[1-[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-3-methylphenyl]-1-ethylpropyl]-2-methyl- (9CI) (CA INDEX NAME)

L3 ANSWER 4 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
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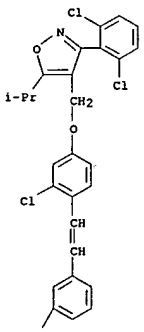
L3 ANSWER 5 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:401885 CAPLUS
DOCUMENT NUMBER: 145:305272
TITLE: New targets in and potential treatments for cholesterol gallstone disease
AUTHOR(S): Doggrell, Sheila A.
CORPORATE SOURCE: Division of Health Practice, Auckland University of Technology, Auckland, N. Z.
SOURCE: Current Opinion in Investigational Drugs (Thomson Scientific) (2006), 7(4), 344-348
CODEN: COIDAZ; ISSN: 1472-4472
PUBLISHER: Thomson Scientific
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. Gallstone disease is very common among American Indians and Hispanics, and approx. 20 million patients are treated for this disease annually in the US. Bile acid receptor (nuclear farnesoid X receptor; FXR) knockout mice fed a lithogenic diet are more susceptible to gallstone disease than wild-type mice. The C57L mouse is also susceptible to gallstone formation when fed a lithogenic diet, and in this model, the small-mol. FXR agonist GW-4064 prevents the precipitation of cholesterol. Bile acids (eg, β-muricholic acid) and their derivs. are also being developed as FXR agonists. Fatty acid bile acid conjugates have the potential to prevent and reverse cholesterol crystallization Furthermore, agents that increase the expression of selected hepatocyte bile acid transporters may also be useful in the treatment of gall bladder disease.
IT 278779-30-9, GW-4064
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(small-mol. FXR GW-4064 prevents precipitation of cholesterol may be useful in gall bladder disease in mouse model)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 5 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
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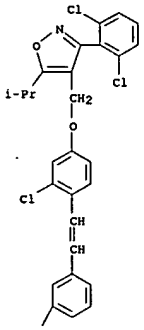
L3 ANSWER 6 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:383580 CAPLUS
DOCUMENT NUMBER: 144:404429
TITLE: A method using farnesoid X receptor (FXR) agonists with PPAR agonists for reducing drug-induced adverse side effects in a patient
INVENTOR(S): Fiorucci, Stefano; Pellicciari, Roberto; Pruzanski, Mark
PATENT ASSIGNEE(S): Intercept Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006044391	A1	20060427	WO 2005-US36536	20051014
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
US 2006252670	A1	20061109	US 2005-250298	20051013
PRIORITY APPLN. INFO.:			US 2004-619381P	P 20041014

AB The invention relates to the discovery that farnesoid X receptor (FXR) agonists can be used in combination with peroxisome proliferation activated receptor γ (PPARγ) agonists to reduce drug-induced adverse side effects in patients suffering from conditions such as insulin resistance, Type II diabetes, metabolic syndrome, non-alc. fatty liver disease (NAFLD), non-alc. steatohepatitis (NASH), and heart disease. Particularly, the invention encompasses methods for treating patients suffering from drug-induced adverse side effects with selective PPARγ, dual PPARα/γ and pan PPARα/γ/δ agonists in combination with FXR agonists.
IT 278779-30-9, GW4064
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(FXR agonist combination with PPAR agonist for reduction of drug-induced adverse effects)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 6 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



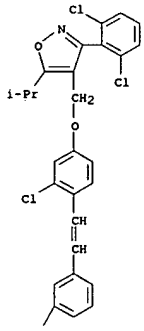
PAGE 2-A

REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 7 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2006:106088 CAPLUS
DOCUMENT NUMBER: 144:251089
TITLE: FXR regulates organic solute transporters α and β in the adrenal gland, kidney, and intestine
AUTHOR(S): Lee, Hans; Zhang, Yanqiao; Lee, Florence Y.; Nelson, Stanley F.; Gonzalez, Frank J.; Edwards, Peter A.
CORPORATE SOURCE: Dep. of Biol. Chem. and Med., Univ. of California, Los Angeles, CA, 90095, USA
SOURCE: Journal of Lipid Research (2006), 47(1), 201-214
CODEN: JLPRAW; ISSN: 0022-2275
PUBLISHER: American Society for Biochemistry and Molecular Biology, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Expression of FXR is largely limited to the liver, intestine, kidney and adrenal gland. However, the role of FXR in the latter two organs is unknown. In the current study, the authors performed microarray anal. using RNA from a human adrenal steroidogenic cell line infected with adenovirus expressing constitutively active FXR (FXRVP16). Several putative FXR target genes were identified, including the organic solute transporters alpha and beta (OSTα and OSTβ). A combinatorial approach utilizing electromobility shift assays and promoter-reporter studies identified two functional FXREs in the human OSTα promoter and one FXRE in the human OSTβ promoter. These elements are conserved in both murine genes. Consistent with these observations the authors demonstrated that treatment of wild-type mice with the synthetic FXR agonist GW4064 resulted in the induction of OSTα and OSTβ mRNA in the intestine and kidney. Both mRNAs were also induced when wild-type, but not FXR-/- murine adrenals were cultured in the presence of GW4064. OSTα and OSTβ mRNA levels were also induced in the adrenal glands and kidneys of wild-type, but not in FXR-/- mice, following elevation of plasma bile acids in response to the hepatotoxin α-naphthylisothiocyanate (ANIT). Finally, the authors demonstrated that co-transfection of cultured H295R cells with expression plasmids encoding OSTα and OSTβ facilitates the uptake of conjugated chenodeoxycholate and activation of FXR target genes. Taken together, these results demonstrate that OSTα and OSTβ are novel FXR target genes that are expressed in the adrenal gland, kidney and intestine. The data also suggest that OSTα and OSTβ may facilitate the transport of conjugated bile acids into steroidogenic cells of the adrenal gland.
IT 278779-30-9, GW4064
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(organic solute transporter genes OSTα and OSTβ are FXR target genes expressed in adrenal gland and intestine and kidney and facilitate transport of conjugated bile acids into adrenal steroidogenic cells)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 7 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 8 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1259663 CAPLUS
DOCUMENT NUMBER: 144:22911
TITLE: Isoxazole compounds as PPAR modulators, their preparation, pharmaceutical compositions, and use in therapy
INVENTOR(S): Epple, Robert; Russo, Ross; Azimioara, Mihai; Xie, Yongping
PATENT ASSIGNEE(S): IRM LLC, Bermuda
SOURCE: PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

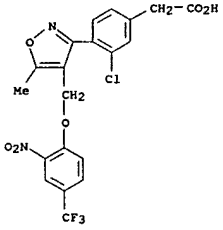
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005113519	A1	20051201	WO 2005-US16672	20050512
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2005245411	A1	20051201	AU 2005-245411	20050512
CA 2564429	A1	20051201	CA 2005-2564429	20050512
EP 1745027	A1	20070124	EP 2005-769154	20050512
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				

PRIORITY APPLN. INFO.: US 2004-571003P P 20040514
WO 2005-US16672 W 20050512

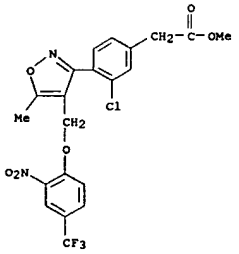
OTHER SOURCE(S): MARPAT 144:22911
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to isoxazole compds. of formula I, which are modulators of peroxisome proliferator-activated receptors (PPAR), particularly PPARδ. In compds. I, R1 is selected from (un)substituted C1-6 alkyl, (un)substituted C3-12 cycloalkyl, (un)substituted C3-8 heterocyclyl, (un)substituted C6-10 aryl, and (un)substituted C5-10 heteroaryl; R2 is selected from (CH2)nO(CH2)nOR5, (CH2)nOR5, CO2R5, C(O)N(R4)2, C(O)N(R4)(CH2)nOR4, CO2(CH2)nOR5, C(O)(CH2)nOR5, C(O)N(R4)(CH2)nOR5, C(O)N(R4)(R5), and C(O)N(R4)(CH2)nR5,



IT 870194-60-8P, [3-Chloro-4-[5-methyl-4-(2-nitro-4-trifluoromethylphenoxymethyl)isoxazol-3-yl]phenyl]acetic acid methyl ester
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate; preparation of isoxazoles as PPAR modulators and their use
for treatment and prevention of diseases associated with PPARδ activity)
RN 870194-60-8 CAPLUS
CN Benzeneacetic acid, 3-chloro-4-[5-methyl-4-[[2-nitro-4-(trifluoromethyl)phenoxy]methyl]-3-isoxazolyl]-, methyl ester (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

where n is 0-4, R4 is H or C1-6 alkyl, and R5 is C1-6 alkyl, C3-12 cycloalkyl, C3-8 heterocyclyl, C6-10 aryl, or C5-10 heteroaryl, or R4 and R5, together with the nitrogen atom to which they are attached, form C3-8 heterocyclyl or C5-10 heteroaryl; and R3 is selected from (un)substituted C3-12 cycloalkyl, (un)substituted C3-8 heterocyclyl, (un)substituted C6-10 aryl, and (un)substituted C5-10 heteroaryl; including pharmaceutically acceptable salts, hydrates, solvates, isomers, and prodrugs thereof. The invention also relates to the prepn. of I, pharmaceutical comps. comprising a therapeutically effective amt. of compd. I in combination with one or more pharmaceutically acceptable excipients, as well as to the use of the compns. to treat or prevent diseases or disorders assocd. with PPAR activity. Esterification of 3-bromophenylacetic acid followed by coupling with cyanide, redn. of the nitrile to an aldehyde, condensation with hydroxylamine, and chlorination gave chlorooxime II. N-Boc-2-bromoethylamine was substituted with 2,4-dichlorophenol followed by deprotection, amidation with Et benzoylacetate to give benzoylacetamide III, which underwent cyclocondensation with chlorooxime II and ester hydrolysis, resulting in the formation of isoxazole IV. Most preferred compds. of the invention express an EC50 value for PPARδ of less than 100 nM. The compds. of the invention are at least 100-fold selective for PPARδ over PPARγ.

IT 870194-58-4P, [3-Chloro-4-[5-methyl-4-(2-nitro-4-trifluoromethylphenoxymethyl)isoxazol-3-yl]phenyl]acetic acid
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of isoxazoles as PPAR modulators and their use
for treatment and prevention of diseases associated with PPARδ activity)
RN 870194-58-4 CAPLUS
CN Benzeneacetic acid, 3-chloro-4-[5-methyl-4-[[2-nitro-4-(trifluoromethyl)phenoxy]methyl]-3-isoxazolyl]- (9CI) (CA INDEX NAME)

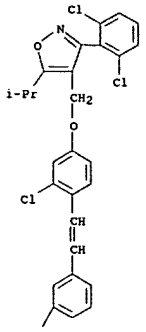
L3 ANSWER 9 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1157460 CAPLUS
DOCUMENT NUMBER: 143:416507
TITLE: Fibroblast growth factor 15 functions as an enterohepatic signal to regulate bile acid homeostasis
AUTHOR(S): Inagaki, Takeshi; Choi, Mihwa; Moschetta, Antonio; Peng, Li; Cummins, Carolyn L.; McDonald, Jeffrey G.; Luo, Guizhen; Jones, Stacey A.; Goodwin, Bryan; Richardson, James A.; Gerard, Robert D.; Repa, Joyce J.; Mangelsdorf, David J.; Kliewer, Steven A.
CORPORATE SOURCE: Department of Molecular Biology, University of Texas Southwestern Medical Center, Dallas, TX, 75390, USA
SOURCE: Cell Metabolism (2005), 2(4), 217-225
CODEN: CMEEB5; ISSN: 1550-4131
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The liver and intestine play crucial roles in maintaining bile acid homeostasis. Fibroblast growth factor 15 (FGF15) signals from intestine to liver to repress the gene encoding cholesterol 7α-hydroxylase (CYP7A1), which catalyzes the first and rate-limiting step in the classical bile acid synthetic pathway. FGF15 expression is stimulated in the small intestine by the nuclear bile acid receptor FXR and represses Cyp7a1 in liver through a mechanism that involves FGF receptor 4 (FGFR4) and the orphan nuclear receptor SHP. Mice lacking FGF15 have increased hepatic CYP7A1 mRNA and protein levels and corresponding increases in CYP7A1 enzyme activity and fecal bile acid excretion. These studies define FGF15 and FGFR4 as components of a gut-liver signaling pathway that synergizes with SHP to regulate bile acid synthesis.

IT 278779-30-9, GW4064
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(FXR agonist; FGF-15 function as enterohepatic signal in regulation of bile acid homeostasis and involved mechanisms)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 9 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A

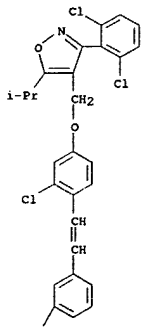


PAGE 2-A

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L3 ANSWER 10 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L3 ANSWER 10 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1077095 CAPLUS
DOCUMENT NUMBER: 143:339369
TITLE: Cross-talk between farnesoid-X-receptor (FXR) and peroxisome proliferator-activated receptor γ contributes to the antifibrotic activity of FXR ligands in rodent models of liver cirrhosis
AUTHOR(S): Fiorucci, Stefano; Rizzo, Giovanni; Antonelli, Elisabetta; Renga, Barbara; Mencarelli, Andrea; Riccardi, Luisa; Morelli, Antonio; Pruzanski, Mark; Pellicciari, Roberto
CORPORATE SOURCE: Dipartimento di Medicina Clinica e Sperimentale, Universita degli Studi di Perugia, Perugia, Italy
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2005), 315(1), 58-68
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The nuclear receptors farnesoid X receptor (FXR) and peroxisome proliferator-activated receptor (PPAR)γ exert counterregulatory effects on hepatic stellate cells (HSCs) and protect against liver fibrosis development in rodents. Here, we investigated whether FXR ligands regulate PPARγ expression in HSCs and models of liver fibrosis induced in rats by porcine serum and carbon tetrachloride administration and bile duct ligation. Our results demonstrate that HSCs trans-differentiation associated with suppression of PPARγ mRNA expression, whereas FXR mRNA was unchanged. Exposure of cells to natural and synthetic ligands of FXR, including 6-Et chenodeoxycholic acid (6-ECDCA), a synthetic derivative of chenodeoxycholic acid, reversed this effect and increased PPARγ mRNA by ≈40-fold. Submaximally effective concns. of FXR and PPARγ ligands were additive in inhibiting α1(I) collagen mRNA accumulation induced by transforming growth factor (TGF)β1. Administration of 6-ECDCA in rats rendered cirrhotic by porcine serum and carbon tetrachloride administration or bile duct ligation reverted down-regulation of PPARγ mRNA expression in HSCs. Cotreatment with 6-ECDCA potentiates the antifibrotic activity of rosiglitazone, a PPARγ ligand, in the porcine serum model as measured by morphometric anal. of liver collagen content, hydroxyproline, and liver expression of α1(I) collagen mRNA, α-smooth muscle actin, fibronectin, TGFβ1, and tissue inhibitor of metalloprotease 1 and 2, whereas it enhanced the expression of PPARγ and uncoupling protein 2, a PPARγ-regulated gene, by 2-fold. In conclusion, by using an in vitro and in vivo and in vivo approach, we demonstrated that FXR ligands up-regulate PPARγ mRNA in HSCs and in rodent models of liver fibrosis. A FXR-PPARγ cascade exerts counter-regulatory effects in HSCs activation.
IT 278779-30-9, GW 4064
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antifibrotic activity of FXR ligands mediated by cross-talk between FXR and PPARγ in rodent liver cirrhosis model)
RN 278779-30-9 CAPLUS
CN Benzoic acid,
3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-

L3 ANSWER 11 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:1049799 CAPLUS
DOCUMENT NUMBER: 143:319188
TITLE: Treatment of fibrosis using farnesoid X receptor (FXR) ligands
INVENTOR(S): Fiorucci, Stefano; Pellicciari, Roberto; Pruzanski, Mark
PATENT ASSIGNEE(S): Intercept Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 70 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

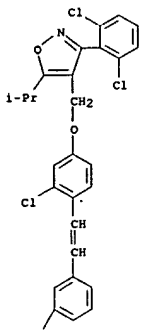
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005089316	A2	20050929	WO 2005-US8575	20050314
WO 2005089316	A3	20060406		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2005222994	A1	20050929	AU 2005-222994	20050314
CA 2559476	A1	20050929	CA 2005-2559476	20050314
US 2006069070	A1	20060330	US 2005-81002	20050314
EP 1734970	A2	20061227	EP 2005-729394	20050314
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR				

PRIORITY APPLN. INFO.: US 2004-552865P P 20040312
WO 2005-US8575 W 20050314

AB The invention discloses a method for inhibiting fibrosis that occurs in an organ where the farnesoid X receptor (FXR) is expressed. The method involves administering a high potency, activating ligand of FXR in an effective amount to a patient who is not suffering from a cholestatic condition. The invention also provides pharmaceutical comps. containing an effective amount of an FXR ligand and kits for dispensing the pharmaceutical comps.
IT 278779-30-9, GW4064
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(farnesoid X receptor ligands for treatment of fibrosis)
RN 278779-30-9 CAPLUS
CN Benzoic acid,
3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-
4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 11 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



PAGE 2-A

L3 ANSWER 12 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:1035522 CAPLUS
DOCUMENT NUMBER: 144:206102
TITLE: VPAC1 expression is regulated by FXR agonists in the human gallbladder epithelium
AUTHOR(S): Chignard, Nicolas; Mergey, Martine; Barbu, Veronique; Finzi, Laetitia; Tiret, Emmanuel; Paul, Annick; Housset, Chantal
CORPORATE SOURCE: Inserm, Paris, Fr.
SOURCE: Hepatology (Hoboken, NJ, United States) (2005), 42(3), 549-557
CODEN: HPTLD9; ISSN: 0270-9139
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Vasoactive intestinal peptide receptor-1 (VPAC1) is the high-affinity receptor of vasoactive intestinal peptide (VIP), a major regulator of bile secretion. To better define the level at which VPAC1 stimulates bile secretion, the authors examined its expression in the different cell types participating in bile formation (i.e., hepatocytes, bile duct, and gallbladder epithelial cells). Because VPAC1 expression was previously shown to be regulated by nuclear receptors, the authors tested the hypothesis that it may be regulated by the farnesoid X receptor (FXR). Quant. RT-PCR and immunoblot analyses of cell isolates indicated that VPAC1 is expressed in all three cell types lining the human biliary tree, with predominant expression in the gallbladder. In primary cultures of human gallbladder epithelial cells, VIP induced cAMP production and chloride secretion. Anal. of the VPAC1 gene revealed the presence of potential FXR response element sequences, and both FXR and RXRα expressions were detected in gallbladder epithelial cells. In these cells, the FXR pharmacol. agonist GW4064 upregulated VPAC1 expression in a dose-dependent manner, and this effect was antagonized by the RXRα ligand, 9-cis retinoic acid. Chenodeoxycholate activated endogenous FXR in gallbladder epithelial cells, as ascertained by electromobility shift assay and upregulation of the FXR target gene, small heterodimer partner. Chenodeoxycholate also provoked an increase in VPAC1 mRNA and protein content in these cells. In conclusion, FXR agonists may increase gallbladder fluid secretion through transcriptional activation of VPAC1, which may contribute to the regulation of bile secretion by bile salts and to a protective effect of FXR pharmacol. agonists in gallstone disease.

IT 278779-30-9, GW4064
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(expression of VPAC1 in different human cells participating in bile formation and regulation by nuclear receptors and their agonists)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 12 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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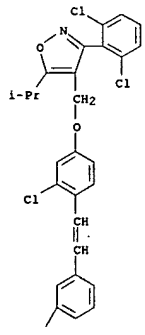

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REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 13 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

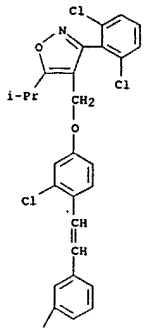
ACCESSION NUMBER: 2005:413517 CAPLUS
DOCUMENT NUMBER: 142:441633
TITLE: Protective effects of 6-ethyl chenodeoxycholic acid, a farnesoid X receptor ligand, in estrogen-induced cholestasis
AUTHOR(S): Fiorucci, Stefano; Clerici, Carlo; Antonelli, Elisabetta; Orlandi, Stefano; Goodwin, Bryan; Sadeghpour, Bahman M.; Sabatino, Giuseppe; Russo, Giuseppe; Castellani, Danilo; Willson, Timothy M.; Pruzanski, Mark; Pellicciari, Roberto; Morelli, Antonio
CORPORATE SOURCE: Clinica di Gastroenterologia ed Epatologia, Dipartimento di Medicina Clinica e Sperimentale Universita degli Studi di Perugia, Perugia, Italy
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2005), 313(2), 604-612
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The farnesoid X receptor (FXR), an endogenous sensor for bile acids, regulates a program of genes involved in bile acid biosynthesis, conjugation, and transport. Cholestatic liver diseases are a group of immunol. and genetically mediated disorders in which accumulation of endogenous bile acids plays a role in the disease progression and symptoms. Here, the authors describe the effect of 6-Et chenodeoxycholic acid (6-ECDCA or INT-747), a semisynthetic bile acid derivative and potent FXR ligand, in a model of cholestasis induced by 5-day administration of 17α-ethynylestradiol (E2 17α) to rats. The exposure of rat hepatocytes to 1 μM 6-ECDCA caused a 3- to 5-fold induction of small heterodimer partner (Shp) and bile salt export pump (bsep) mRNA and 70 to 80% reduction of cholesterol 7α-hydroxylase (cyp7a1), oxysterol 12β-hydroxylase (cyp8b1), and Na+/taurocholate cotransporting peptide (ntcp). In vivo administration of 6-ECDCA protects against cholestasis induced by E2 17α. Thus, 6-ECDCA reverted bile flow impairment induced by E2 17α, reduced secretion of cholic acid and deoxycholic acid, but increased muricholic acid and chenodeoxycholic acid secretion. In vivo administration of 6-ECDCA increased liver expression of Shp, bsep, multidrug resistance-associated protein-2, and multidrug resistance protein-2, whereas it reduced cyp7a1 and cyp8b1 and ntcp mRNA. These changes were reproduced by GW4064, a synthetic FXR ligand. In conclusion, by demonstrating that 6-ECDCA protects against E2 17α cholestasis, the authors' data support the notion that development of potent FXR ligands might represent a new approach for the treatment of cholestatic disorders.

IT 278779-30-9, GW4064
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); BIOL (Biological study)
(chenodeoxycholic acid derivative protection against estrogen-induced cholestasis and mechanisms thereof)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 13 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
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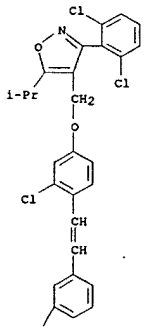
L3 ANSWER 14 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L3 ANSWER 14 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:413351 CAPLUS
DOCUMENT NUMBER: 142:444987
TITLE: The human organic anion transporter 2 gene is transactivated by hepatocyte nuclear factor-4α and suppressed by bile acids
AUTHOR(S): Popowski, Katrin; Eloranta, Jyrki J.; Saborowski, Michael; Fried, Michael; Meier, Peter J.; Kullak-Ublick, Gerd A.
CORPORATE SOURCE: Laboratory of Molecular Gastroenterology and Hepatology, University Hospital, Zurich, Switz.
SOURCE: Molecular Pharmacology (2005), 67(5), 1629-1638
CODEN: MOPHA3; ISSN: 0026-895X
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The human organic anion transporter 2 (hOAT2, SLC22A7) mediates the sodium-independent uptake of numerous drugs, including cephalosporins, salicylates, dicarboxylates, and prostaglandins, and is mainly expressed in hepatocytes. Because the regulation of hOAT2 expression is poorly understood, we characterized cis-acting elements in the 5'-flanking region that regulate hOAT2 transcription. A consensus binding motif for the hepatocyte nuclear factor-4α (HNF-4α), arranged as a direct repeat (DR)-1, is located at nucleotides -329/-317 relative to the transcription initiation site. This element specifically binds HNF-4α in electrophoretic mobility shift assays. A luciferase-linked hOAT2 promoter fragment containing the HNF-4α binding site was transactivated upon cotransfection of an HNF-4α expression vector in Huh7 cells, whereas site-directed mutagenesis of the DR-1 element abolished activation by HNF-4α. Short interfering RNAs inhibiting endogenous HNF-4α expression markedly reduced endogenous expression of hOAT2 in Huh7 cells. Because HNF-4α is a known target for bile acid-mediated repression of gene transcription, we studied whether chenodeoxycholic acid (CDCA) suppresses hOAT2 gene expression by inhibiting HNF-4α-mediated transactivation. Treatment of Huh7 cells with CDCA or the synthetic farnesoid X receptor (FXR) agonist GW 4064 decreased mRNA and protein levels and also nuclear binding activity of HNF-4α. The FXR-inducible transcriptional repressor small heterodimer partner inhibited transactivation of hOAT2 promoter constructs and of endogenous hOAT2 expression by HNF-4α. We conclude that the hOAT2 gene is critically dependent on HNF-4α and that bile acids repress the hOAT2 gene by inhibiting HNF-4α. Hepatic uptake of hOAT2 substrates may thus be decreased in disease conditions associated with elevated intracellular levels of bile acids.
IT 278779-30-9, GW 4064
RL: PAC (Pharmacological activity); BIOL (Biological study)
(human organic anion transporter 2 gene transactivation by HNF-4α and suppression by bile acids via HNF-4α inhibition in hepatocytes and mechanisms therein)
RN 278779-30-9 CAPLUS
CN Benzoic acid,
3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-

L3 ANSWER 15 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:316356 CAPLUS
DOCUMENT NUMBER: 142:367666
TITLE: Compositions and methods using farnesoid X receptor agonists for treatment of fibrosis
INVENTOR(S): Liu, Yaping; Moore, John Tomlin
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA; Jones, Stacey Ann
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2005032549	A1	20050414	WO 2004-US29748	20040910
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1696910	A1	20060906	EP 2004-783821	20040910
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK, HR				
US 2007015796	A1	20070118	US 2006-572974	20060322
PRIORITY APPLN. INFO.:			US 2003-506394P	P 20030926
			WO 2004-US29748	W 20040910

OTHER SOURCE(S): MARPAT 142:367666
AB Methods for the treatment of fibrosis, including liver fibrosis, via administration of FXR agonists are provided. FXR agonist GW4064 reduced collagen deposition in livers of rats treated with CCl4.
IT 278779-30-9, GW4064
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(as farnesoid X receptor agonist; farnesoid X receptor agonists for treatment of fibrosis)
RN 278779-30-9 CAPLUS
CN Benzoic acid,
3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 15 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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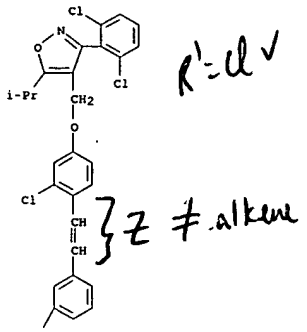

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REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

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L3 ANSWER 16 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:304966 CAPLUS
DOCUMENT NUMBER: 143:2829
TITLE: Molecular Dynamics Simulation of the Ligand Binding Domain of Farnesoid X Receptor. Insights into Helix-12 Stability and Coactivator Peptide Stabilization in Response to Agonist Binding
AUTHOR(S): Costantino, Gabriele; Entrena-Guadix, Antonio; Macchiarulo, Antonio; Gioiello, Antimo; Pellicciari, Roberto
CORPORATE SOURCE: Dipartimento di Chimica e Tecnologia del Farmaco, Universita di Perugia, Perugia, 06123, Italy
SOURCE: Journal of Medicinal Chemistry (2005), 48(9), 3251-3259
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English

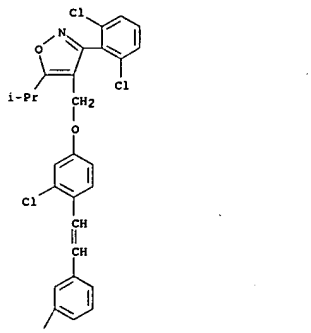
AB The dynamic changes which take place in the ligand binding domain (LBD) of farnesoid X receptor (FXR) in response to agonist binding and in the presence of coactivator peptides were studied with nanosecond time-scale mol. dynamics. Four different systems were analyzed, including the holo-LBD complexed with 6ECDCA, the holo-LBD in the presence of two coactivator peptides, and two artificial apo forms, with and without coactivator peptides. Our results revealed a detailed picture of the differential micro- and macromodifications occurring in the LBD in the presence or not of the agonist mol. and the coactivator peptides. In the apo simulation a major conformational change took place in the crucial helix 12, while the holo-LBD was globally stabilized by the ligand. When the coactivator peptides were included in the simulation, a clear agonist-induced stabilization was observed for the canonical peptide. Interestingly, the second peptide was released from the holo-LBD while it was kept bound in the apo simulation. The present results provide a mol. basis for the understanding the role played by the bile acid agonist in receptor stabilization and enhanced cofactor recruitments.

IT 278779-30-9, GW4064
RL: BSU (Biological study, unclassified); BIOL (Biological study) (mol. dynamics simulation of ligand binding domain of farnesoid X receptor)

RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 16 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



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REFERENCE COUNT: 27 THERE ARE 27 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE

FORMAT

L3 ANSWER 17 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2005:256245 CAPLUS
DOCUMENT NUMBER: 143:71126
TITLE: A Nuclear Receptor Ligand Down-Regulates Cytosolic Phospholipase A2 Expression to Reduce Bile Acid-Induced Cyclooxygenase 2 Activity in Cholangiocytes: Implications of Anticarcinogenic Action of Farnesoid X Receptor Agonists
AUTHOR(S): Komichi, Daisuke; Tazuma, Susumu; Nishioka, Tomoji; Hyogo, Hideyuki; Chayama, Kazuaki
CORPORATE SOURCE: Departments of Medicine and Molecular Science, Hiroshima University, Hiroshima, Japan
SOURCE: Digestive Diseases and Sciences (2005), 50(3), 514-524
CODEN: DDSCDJ; ISSN: 0163-2116
PUBLISHER: Springer Science+Business Media, Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

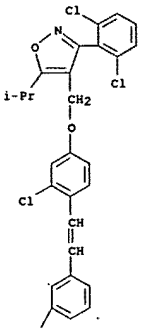
AB Bile acids are considered to be involved in the development of biliary tract carcinoma, although the underlying mechanisms are yet to be established. The aims of this study were (1) to investigate the carcinogenic role of bile acids in the biliary system based on the arachidonate-prostanoid pathway and (2) to clarify the therapeutic role of a farnesoid X receptor (FXR) ligand that modifies bile acid metabolism Immortalized mouse cholangiocytes were incubated with glycochenodeoxycholate (GCDC), taurocholate, taurochenodeoxycholate, taurodeoxycholate, and tauroursodeoxycholate. GCDC induced cyclooxygenase 2 (COX-2) expression (Western blotting, 1.7-fold; RT-PCR, 2.3-fold) and prostaglandin (PG) production (PGE2, 6.3-fold; PGF2α, 8.5-fold), whereas cytosolic phospholipase A2 (cPLA2) expression and activity were reduced. In contrast, no marked changes were induced by the other bile acids. When the same experiment was performed in the presence of a synthetic FXR ligand (GW4064), cPLA2 expression and activity were reduced, although COX-2 expression was unchanged. GW4064 also suppressed PG generation by 40%. In conclusion, the present findings suggest a carcinogenic potential of GCDC. A synthetic FXR ligand (GW4064) inhibited the induction of COX-2 activity (detected as PG production) by GCDC, suggesting its anticarcinogenic potential. This effect seemed to be due to down-regulation of cPLA2. FXR ligands may have therapeutic potential against biliary carcinogenesis, but a delivery system for these agents is still to be developed.

IT 278779-30-9, GW4064
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(synthetic farnesoid X receptor agonist GW4064 down regulated cytosolic phospholipase A2 expression and activity to reduce glycochenodeoxycholate-induced cyclooxygenase 2 activity in immortalized mouse cholangiocytes)

RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 17 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



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REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS
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L3 ANSWER 18 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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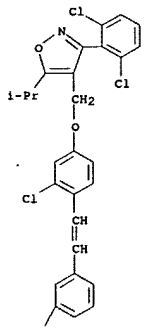

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REFERENCE COUNT: 47 THERE ARE 47 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
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L3 ANSWER 18 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2005:233216 CAPLUS
DOCUMENT NUMBER: 142:291878
TITLE: Regulation of carbohydrate metabolism by the farnesoid X receptor
AUTHOR(S): Stayrook, Keith R.; Bramlett, Kelli S.; Savkur, Rajesh S.; Ficorilli, James; Cook, Todd; Christe, Michael E.; Michael, Laura F.; Burris, Thomas P.
CORPORATE SOURCE: Lilly Research Laboratories, Lilly Corporate Center, Indianapolis, IN, 46285, USA
SOURCE: Endocrinology (2005), 146(3), 984-991
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The farnesoid X receptor (FXR; NR1H4) is a nuclear hormone receptor that functions as the bile acid receptor. In addition to the critical role FXR plays in bile acid metabolism and transport, it regulates a variety of genes important in lipoprotein metabolism We demonstrate that FXR also plays a role in carbohydrate metabolism via regulation of phosphoenolpyruvate carboxykinase (PEPCK) gene expression. Treatment of either H4IIE or MH1C1 rat hepatoma cell lines as well as primary rat or human hepatocytes with FXR agonists led to stimulation of PEPCK mRNA expression to levels comparable to those obtained with glucocorticoid receptor agonists. We examined the physiol. significance of FXR agonist-induced enhancement of PEPCK expression in primary rat hepatocytes. In addition to inducing PEPCK expression in primary hepatocytes, FXR agonists stimulated glucose output to levels comparable to those observed with a glucocorticoid receptor agonist. Consistent with these observations, treatment of C57BL6 mice with GW 4064 significantly increased hepatic PEPCK expression. Activation of FXR initiated a cascade involving induction of peroxisome proliferator-activated receptor α and TRB3 expression that is consistent with stimulation of PEPCK gene expression via interference with a pathway that may involve Akt-dependent phosphorylation of Forkhead/winged helix transcription factor (FOXO1). The FXR-peroxisome proliferator-activated receptor α-TRB3 pathway was conserved in rat hepatoma cell lines, mice, as well as primary human hepatocytes. Thus, in addition to its role in the regulation of lipid metabolism, FXR regulates carbohydrate metabolism

IT 278779-30-9, GW 4064
RL: PAC (Pharmacological activity); BIOL (Biological study)
(farnesoid X receptor regulation of carbohydrate metabolism in liver and signaling therein)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 19 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:1124587 CAPLUS
DOCUMENT NUMBER: 142:69188
TITLE: Combination therapy for the treatment of diabetes
INVENTOR(S): Erondu, Ngozi E.; Fong, Tung M.; MacNeil, Douglas J.; Van Der Ploeg, Leonardus H. T.; Kanatani, Akio
PATENT ASSIGNEE(S): Merck & Co., Inc., USA; Banyu Pharmaceutical Co., Ltd.
SOURCE: PCT Int. Appl., 109 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004110375	A2	20041223	WO 2004-US17291	20040602
WO 2004110375	A3	20050512		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1635832	A2	20060322	EP 2004-753999	20040602
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, FI, RO, CY, TR, BG, CZ, EE, HU, PL, SK				

PRIORITY APPLN. INFO.: US 2003-476388P P 20030606
WO 2004-US17291 W 20040602

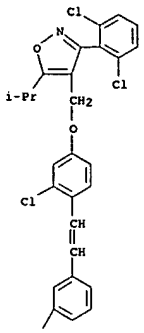
OTHER SOURCE(S): MARPAT 142:69188

AB The present invention relates to compns. comprising an anti-obesity agent and an anti-diabetic agent useful for the treatment of diabetes, diabetes associated with obesity and diabetes-related disorders. The present invention further relates to methods of treating or preventing obesity, and obesity-related disorders, in a subject in need thereof by administering a composition of the present invention. The present invention further provides for pharmaceutical compns., medicaments, and kits useful in carrying out these methods.

IT 278779-30-9, GW 4064
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy of diabetes and diabetes-related disorders using antiobesity agent and antidiabetic agent and other agents)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 19 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



PAGE 2-A

L3 ANSWER 20 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:1124581 CAPLUS
DOCUMENT NUMBER: 142:69181
TITLE: Combination therapy for the treatment of hypertension
INVENTOR(S): Fong, Tung M.; Erondu, Ngozi E.; Macneil, Douglas J.; Mcintyre, James H.; Van Der Ploeg, Leonardus H. T.
PATENT ASSIGNEE(S): Merck & Co., Inc., USA
SOURCE: PCT Int. Appl., 99 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004110368	A2	20041223	WO 2004-US17090	20040602
WO 2004110368	A3	20060720		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW: BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
EP 1635773	A2	20060322	EP 2004-753832	20040602
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
US 2006160834	A1	20060720	US 2005-559111	20051202
PRIORITY APPLN. INFO.:			US 2003-476390P	P 20030606
			WO 2004-US17090	W 20040602

OTHER SOURCE(S): MARPAT 142:69181

AB The present invention relates to compns. comprising an anti-obesity agent and an anti-hypertensive agent useful for the treatment of hypertension, hypertension associated with obesity, and hypertension-related disorders. The present invention further relates to methods of treating or preventing obesity, and obesity-related disorders, in a subject in need thereof by administering a composition of the present invention. The present invention further provides for pharmaceutical compns., medicaments, and kits useful in carrying out these methods.

IT 278779-30-9, GW 4064
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination therapy of hypertension and hypertension-related disorders using antiobesity agent and antihypertensive agent and other agents and antihypertensive agent)

RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 20 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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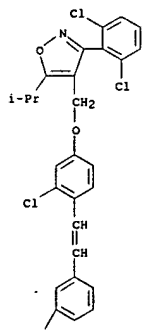


PAGE 2-A

L3 ANSWER 21 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:1066210 CAPLUS
DOCUMENT NUMBER: 142:192933
TITLE: Application of QSAR analysis to organic anion transporting polypeptide 1a5 (Oatpla5) substrates
AUTHOR(S): Yarim, Mine; Moro, Stefano; Huber, Robert; Meier, Peter J.; Kaseda, Chosei; Kashima, Toru; Hagenbuch, Bruno; Folkers, Gerd
CORPORATE SOURCE: Institute of Pharmaceutical Sciences, D-ANBI, ETH Zurich, Zurich, CH-8057, Switz.
SOURCE: Bioorganic & Medicinal Chemistry (2004), Volume Date 2005, 13(2), 463-471
CODEN: BMECEP; ISSN: 0968-0896
PUBLISHER: Elsevier Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

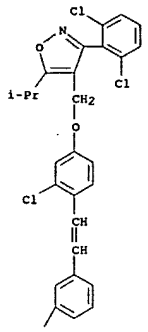
AB Organic anion transporting polypeptide 1a5, Slcola5 (previously called Oatp3, Slc21a7) is a multispecific transmembrane transport protein that belongs to the OATP/SLCO superfamily of solute carriers. It is expressed in several epithelial barriers such as the small intestine and the choroid plexus where it might play an important role in the disposition of numerous endogenous and exogenous organic compds. Since the mol. basis of the multispecificity of Oatpla5 is not known and the three-dimensional structure not solved yet, we used three-dimensional quant. structure-activity relationship (3D-QSAR) techniques to obtain topol. information on the substrate binding site of the protein. We aligned a heterogeneous data set of 18 Oatpla5 substrates using the Genetic Algorithm Similarity Program (GASP) and performed comparative mol. field anal. (CoMFA) using this alignment. This resulted in a reasonable QSAR model including steric and electrostatic fields with a leave-one-out cross-validated r2cv value of 0.705 and a no-cross-validated regression coefficient r2 value of 0.949. Based on the derived model we identified new potential Oatpla5 substrates and confirmed their predicted apparent affinity values exptl.

IT 278779-30-9, GW4064
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(application of QSAR anal. to organic anion transporting polypeptide 1a5 substrates)

RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 21 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



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REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L3 ANSWER 22 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:1061036 CAPLUS
DOCUMENT NUMBER: 142:232933
TITLE: The nuclear receptor SHP mediates inhibition of hepatic stellate cells by FXR and protects against liver fibrosis
AUTHOR(S): Fiorucci, Stefano; Antonelli, Elisabetta; Rizzo, Giovanni; Renga, Barbara; Mencarelli, Andrea; Riccardi, Luisa; Orlandi, Stefano; Pellicciari, Roberto; Morelli, Antonio
CORPORATE SOURCE: Dipartimento di Medicina Clinica e Sperimentale, Clinica di Gastroenterologia ed Endoscopia Digestiva, Perugia, Italy
SOURCE: Gastroenterology (2004), 127(5), 1497-1512
CODEN: GASTAB; ISSN: 0016-5085
PUBLISHER: Elsevier Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background & Aims: The farnesoid X receptor (FXR) is an endogenous sensor for bile acids and inhibits bile acid synthesis by inducing small heterodimer partner (SHP) gene expression. The aim of this study was to investigate whether FXR is expressed by and modulates function of hepatic stellate cells (HSCs). Methods: The antifibrotic activity of FXR ligand was tested in 2 rodent models: the porcine serum and bile duct ligation (BDL). Results: Twelve-week administration of 1-10 mg/kg 6-Et chenodeoxycholic acid (6-ECDCA), a synthetic FXR ligand, to porcine serum-treated rats prevented liver fibrosis development and reduced liver expression of α1(I) collagen, TGF-β1 and α-SMA mRNA by .apprx.90%. Therapeutic administration of 6-ECDCA, 3 mg/kg, to BDL rats reduced liver fibrosis and α1(I) collagen, transforming growth factor (TGF)-β1, α-SMA, and tissue metalloproteinase inhibitor (TIMP)-1 and 2 mRNA (mRNA) by 70%-80%. No protection was observed in BDL rats treated with CDCA, 3 mg/kg, and ursodeoxycholic acid, 15 mg/kg. FXR expression was detected in HSCs. Exposure of HSCs to FXR ligands caused a
3-fold increase of SHP, reduced α1(I)collagen and TGF-β1 by .apprx.60%-70% and abrogates α1(I) collagen mRNA up-regulation induced by thrombin and TGF-β1. By retrovirus infection and small interference RNA, we generated SHP overexpressing and SHP-deficient HSC-T6. Using these cell lines, we demonstrated that SHP binds JunD and inhibits DNA binding of adaptor protein (AP)-1 induced by thrombin. Conclusions: By demonstrating that an FXR-SHP regulatory cascade promotes resolution of liver fibrosis, this study establish that FXR ligands might represent a novel therapeutic option to treat liver fibrosis.
IT 278779-30-9, GW4064
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(GW4064 reduced α1(1) collagen in HSCs and immortalized HSP-T6 cell line)
RN 278779-30-9 CAPLUS
CN Benzoic acid,
3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 22 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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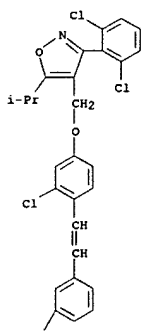

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L3 ANSWER 23 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:1041398 CAPLUS
DOCUMENT NUMBER: 142:32776
TITLE: Prevention of cholesterol gallstone disease by FXR agonists in a mouse model
AUTHOR(S): Moschetta, Antonio; Bookout, Angie L.; Mangelsdorf, David J.
CORPORATE SOURCE: Howard Hughes Medical Institute and Department of Pharmacology, University of Texas Southwestern Medical
Center, Dallas, TX, 75390-9050, USA
SOURCE: Nature Medicine (New York, NY, United States) (2004), 10(12), 1352-1358
CODEN: NAMEFI; ISSN: 1078-8956
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cholesterol gallstone disease is characterized by several events, including cholesterol precipitation in bile, increased bile salt hydrophobicity
and gallbladder inflammation. Here, we describe the same phenotype in mice lacking the bile acid receptor, FXR. Furthermore, in susceptible wild-type mice that recapitulate human cholesterol gallstone disease, treatment with a synthetic FXR agonist prevented sequelae of the disease. These effects were mediated by FXR-dependent increases in biliary bile salt and phospholipid concns., which restored cholesterol solubility and thereby prevented gallstone formation. Taken together, these results indicate that FXR is a promising therapeutic target for treating or preventing cholesterol gallstone disease.
IT 278779-30-9, GW 4064
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(prevention of cholesterol gallstone disease by FXR agonists in a mouse model)
RN 278779-30-9 CAPLUS
CN Benzoic acid,
3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 23 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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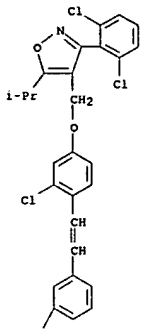

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RECORD. ALL CITATIONS AVAILABLE IN THE RE
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L3 ANSWER 24 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:813951 CAPLUS
DOCUMENT NUMBER: 142:150431
TITLE: Structural and biochemical analysis of bile acid receptor fxr
AUTHOR(S): Mi, Li-Zhi
CORPORATE SOURCE: Univ. of Virginia, Charlottesville, VA, USA
SOURCE: (2004) 152 pp. Avail.: UMI, Order No. DA3108812 From: Diss. Abstr. Int., B 2004, 64(10), 4879
DOCUMENT TYPE: Dissertation
LANGUAGE: English
AB Unavailable
IT 278779-30-9, GW4064
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(structural and biochem. anal. of bile acid receptor fxr)
RN 278779-30-9 CAPLUS
CN Benzoic acid,
3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

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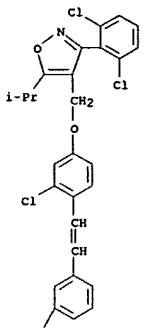

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L3 ANSWER 24 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

L3 ANSWER 25 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 2004:792517 CAPLUS
DOCUMENT NUMBER: 142:213172
TITLE: Regulation of CYP3A4 by the bile acid receptor FXR: evidence for functional binding sites in the CYP3A4 gene
AUTHOR(S): Gnerre, Carmela; Blaettler, Sharon; Kaufmann, Michel R.; Looser, Renate; Meyer, Urs A.
CORPORATE SOURCE: Division of Pharmacology and Neurobiology, Biozentrum of the University of Basel, Basel, CH-4056, Switz.
SOURCE: Pharmacogenetics (2004), 14(10), 635-645
CODEN: PHMCEE; ISSN: 0960-314X
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB CYP3A4, the most abundant cytochrome P 450 in human liver, is responsible for the metabolism of numerous xenobiotics and endobiotics. CYP3A4 expression
is highly variable and is induced by numerous compds. of exogenous and endogenous origin, including elevated concns. of secondary bile acids via the pregnane X receptor (PXR). Authors show that physiol. concns. of the primary bile acid chenodeoxycholic acid regulate the expression of CYP3A4 via the bile acid receptor FXR. Expts. performed in vitro in different cell culture systems, gel-mobility shift assays and expts. performed in vivo in transgenic mice lacking FXR or PXR and treated with the synthetic FXR agonist GW4064 were undertaken to study the implication of FXR in the regulation of CYP3A. The data provide evidence for the presence of two functional FXR recognition sites located in a 345-bp element within the 5'-flanking region of CYP3A4. Mutational anal. of these sites and expts. in transgenic mice lacking FXR or PXR support the relevance of FXR activation for CYP3A regulation. Thus, whereas elevated concns. of precursors of bile acids and secondary bile acids induce CYP3A via PXR, primary bile acids can modulate the expression of CYP3A via FXR. These findings may explain elevated CYP3A expression in cholestasis and part of the variability of drug responsiveness and toxicity between individuals.
IT 278779-30-9, GW4064
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(regulation of CYP3A4 by the bile acid receptor FXR and evidence for functional binding sites in the CYP3A4 gene)
RN 278779-30-9 CAPLUS
CN Benzoic acid,
3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 25 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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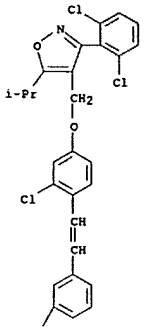

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REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS
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L3 ANSWER 26 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:630391 CAPLUS
DOCUMENT NUMBER: 142:273060
TITLE: The nuclear bile acid receptor FXR as a novel therapeutic target in cholestatic liver diseases: Hype or hope?
AUTHOR(S): Trauner, Michael
CORPORATE SOURCE: Laboratory of Experimental and Molecular Hepatology, Division of Gastroenterology and Hepatology, Department of Internal Medicine, Medical University Graz, Graz, Austria
SOURCE: Hepatology (Hoboken, NJ, United States) (2004), 40(1), 260-263
CODEN: HPTLD9; ISSN: 0270-9139
PUBLISHER: John Wiley & Sons, Inc.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review. A polemic in response to Liu et al. (J. Clin. Invest., 2003, 112, 1678-1687) is presented. Liu et al. investigated the effects of the farnesoid X receptor agonist GW4064 and tauroursodeoxycholic acid (TUDCA) as clin. comparator in α-naphthylisothiocyanate (ANIT)-treated and common bile duct ligated (CBDL) rats as models of intrahepatic and extrahepatic cholestasis, resp. Some of conceptual and methodol. limitations of the study of Liu et al. are discussed. However, despite these limitations, their study indicates an important new direction in the treatment of cholestasis. This concept needs to be refined by the use of more gene-selective agonists and combination approaches targeting both regular/orthograde (FXR-dependent) and alternative/retrograde pathways of bile acid transport and metabolism
IT 278779-30-9, GW4064
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses) (nuclear bile acid receptor FXR as therapeutic target in cholestatic liver diseases)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 26 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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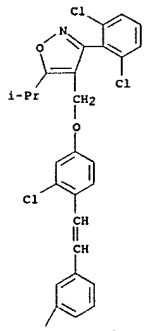

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REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
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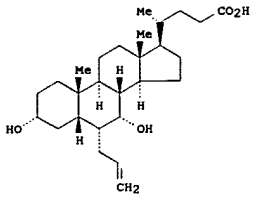
L3 ANSWER 27 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:587458 CAPLUS
DOCUMENT NUMBER: 141:277805
TITLE: Bile Acid Derivatives as Ligands of the Farnesoid X Receptor. Synthesis, Evaluation, and Structure-Activity Relationship of a Series of Body and Side Chain Modified Analogues of Chenodeoxycholic Acid
AUTHOR(S): Pellicciari, Roberto; Costantino, Gabriele; Camaioni, Emidio; Sadeghpour, Bahman M.; Entrena, Antonio; Willson, Timothy M.; Fiorucci, Stefano; Clerici, Carlo; Gioiello, Antimo
CORPORATE SOURCE: Dipartimento di Chimica e Tecnologia del Farmaco, Universita di Perugia, Perugia, 06123, Italy
SOURCE: Journal of Medicinal Chemistry (2004), 47(18), 4559-4569
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 141:277805
GI

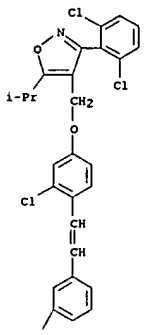


I

AB The farnesoid X receptor (FXR) is activated by endogenous bile acids (BAs) and plays a variety of physiol. roles related to modulation of gene transcription. In particular, FXR pos. regulates the cholesterol catabolism while feedback inhibits the BA synthesis by repressing the expression of the CYP7A and CYP8B genes. The authors have previously shown that 6α-ethyl-CDCA (6ECDCA) is a potent and selective FXR agonist. In this paper the authors report an extensive structure-activity relationship for a series of synthetic bile acids, e.g. I. The results indicate that the 6α position plays a fundamental role in determining affinity and that the side chain of BA is amenable to a variety of chemical modification. Although none of the new derivs. is more potent than 6ECDCA, we show here that a wide variability in efficacy, from full agonists to partial antagonists, can be obtained.
IT 278779-30-9
RL: PAC (Pharmacological activity); BIOL (Biological study) (synthesis, evaluation, and structure-activity relationship of a

L3 ANSWER 27 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
of body and side chain modified analogs of chenodeoxycholic acid as ligands of the farnesoid X receptor)
RN 278779-30-9 CAPLUS
CN Benzoic acid,
3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS
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L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:467875 CAPLUS
DOCUMENT NUMBER: 141:23525
TITLE: Preparation of isoxazole derivs. as farnesoid x receptor agonists
INVENTOR(S): Boggs, Sharon D.; Collins, Jon L.; Hyatt, Stephen M.; Maloney, Patrick R.
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: PCT Int. Appl., 124 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

Instant App.

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004048349	A1	20040610	WO 2003-US35808	20031112
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RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
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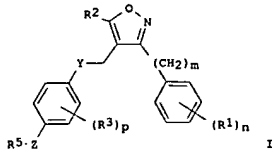
EP 1562915	A1	20050817	EP 2003-783282	20031112
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				
JP 2006515838	T	20060608	JP 2004-555406	20031112
US 2006258725	A1	20061116	US 2005-535228	20050517
PRIORITY APPLN. INFO.:			US 2002-428374P	P 20021122
			WO 2003-US35808	W 20031112

OTHER SOURCE(S): MARPAT 141:23525
GI

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



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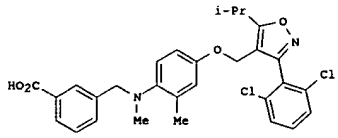

II

AB The title compds. I [R1 = halo, alkyl, alkenyl, cyano, etc.; R2 = alkyl, alkenyl, cycloalkyl, cycloalkenyl, etc.; Y = -O-, -N(R7)-; R3 = halo, alkyl, alkenyl, alkynyl, cycloalkyl, cycloalkenyl, etc.; Z = -OR4-, -R4O-, -S(O)qR4-; -R4S(O)q-, etc.; R4 = alkylene or alkenylene; R5 = R6O-, R6O2C-, and (R9)r-A-, where A = aryl, or 5-12 membered heterocycle or heteroaryl; R6 = H, alkyl, alkenyl, cycloalkyl, cycloalkenyl; R7 = H, or alkyl; R9 = halo, alkyl, alkenyl, alkynyl, cycloalkyl, etc.; m = 0-3; n = 1-5; p = 0-4; r = 0-4] were prepared as as farnesoid x receptor agonists for the treatment or prevention of FXR mediated diseases or conditions, including cardiovascular disease and atherosclerosis (no data). For example, reaction of N-(4-([3-(2,6-dichlorophenyl)-5-isopropylisoxazol-4-yl]methoxy]-2-methylphenyl)-N-methylamine (preparation given) with Me 3-(bromomethyl]benzoate followed by treatment of aqueous lithium hydroxide furnished compound II. The latter displayed activity against human farnesoid X receptor alpha with pEC50 value > 7.
IT 700835-02-5P 700835-14-9P
RL: PAC (Pharmacological activity); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(Preparation of isoxazole derivs. as farnesoid x receptor agonists)
RN 700835-02-5 CAPLUS
CN Benzoic acid,
4-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]amino]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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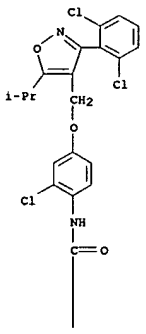

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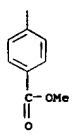

RN 700835-14-9 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]amino]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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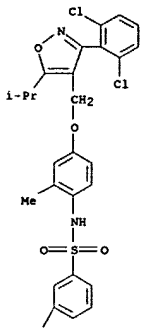

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700835-01-4P 700835-03-6P 700835-04-7P
700835-05-8P 700835-06-9P 700835-07-0P
700835-08-1P 700835-09-2P 700835-10-5P
700835-11-6P 700835-12-7P 700835-13-8P
700835-15-0P 700835-16-1P 700835-17-2P
700835-18-3P 700835-19-4P 700835-20-7P
700835-21-8P 700835-22-9P 700835-23-0P
700835-24-1P 700835-25-2P 700835-26-3P
700835-27-4P 700835-28-5P 700835-29-6P
700835-30-9P 700835-31-0P 700835-32-1P

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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RN 700834-80-6 CAPLUS
CN Benzoic acid, 4-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]methyl]-, methyl ester (9CI) (CA INDEX NAME)

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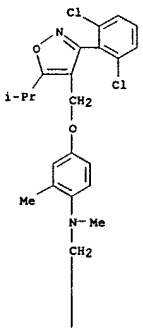

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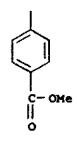

RN 700834-81-7 CAPLUS
CN Benzoic acid,
3-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]amino]methyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

700835-33-2P 700835-34-3P 700835-35-4P
700835-36-5P 700835-37-6P 700835-38-7P
700835-39-8P 700835-40-1P 700835-41-2P
700835-42-3P 700835-43-4P 700835-44-5P
700835-45-6P 700835-46-7P 700835-47-8P
700835-48-9P 700835-49-0P 700835-50-3P
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700835-69-4P 700835-70-7P 700835-71-8P
700835-72-9P 700835-73-0P 700835-74-1P
700835-75-2P 700835-76-3P 700835-77-4P
700835-78-5P 700835-79-6P 700835-80-9P
700836-32-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(Prepn. of isoxazole derivs. as farnesoid x receptor agonists)

RN 700834-79-3 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]methyl]- (9CI) (CA INDEX NAME)

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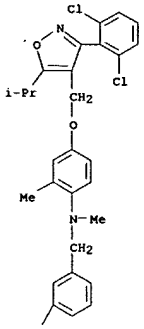

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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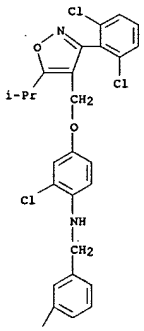

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RN 700834-82-8 CAPLUS
CN 2-Furancarboxylic acid,
5-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]methyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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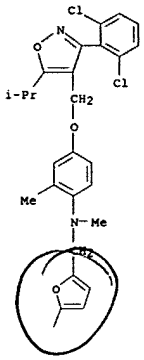

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RN 700834-83-9 CAPLUS
CN Benzoic acid, 4-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]methyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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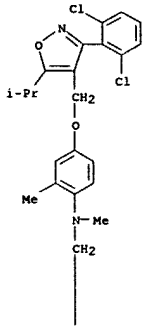

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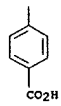
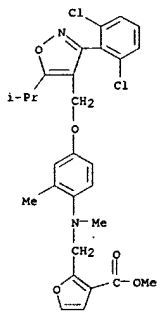


RN 700834-84-0 CAPLUS
CN 3-Furancarboxylic acid, 2-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]methyl]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 700834-85-1 CAPLUS
CN 2,1,3-Benzoxadiazole-5-methanamine, N-[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]-N-methyl- (9CI) (CA INDEX NAME)

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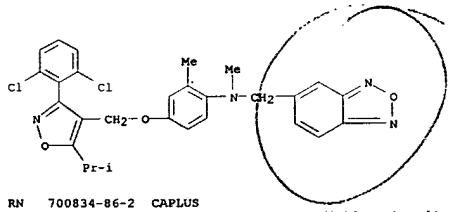

RN 700834-86-2 CAPLUS
CN Benzenemethanamine, N-[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]-N-methyl-4-(1,2,3-thiadiazol-4-yl)- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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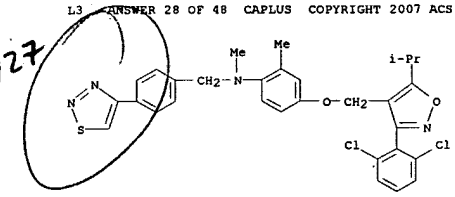

1,2,3 thiadiazol

RN 700834-87-3 CAPLUS
CN Benzonitrile, 4-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]methyl]- (9CI) (CA INDEX NAME)

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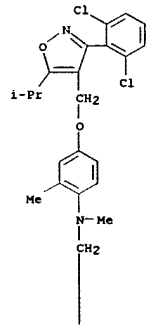

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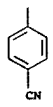
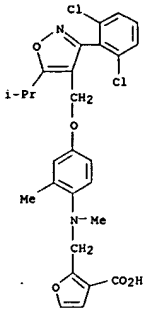


L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

RN 700834-88-4 CAPLUS
CN 3-Furancarboxylic acid, 2-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]methyl]- (9CI) (CA INDEX NAME)



RN 700834-89-5 CAPLUS
CN Benzenemethanol, 3-[[[4-[[3-[(2,6-dichlorophenyl)methyl]-5-ethyl-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]methyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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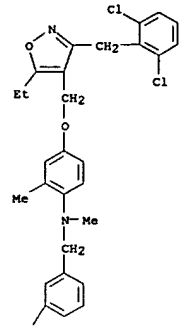

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RN 700834-90-8 CAPLUS
CN Benzenemethanol, 4-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]methyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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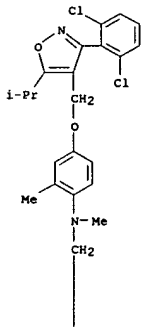

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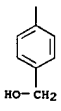

RN 700834-91-9 CAPLUS
CN Benzoic acid, 3-[[methyl[2-methyl-4-[[5-(1-methylethyl)-3-(2,4,6-trichlorophenyl)-4-isoxazolyl]methoxy]phenyl]amino]methyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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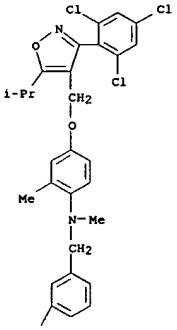

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RN 700834-92-0 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-[(2,6-dichlorophenyl)methyl]-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]methyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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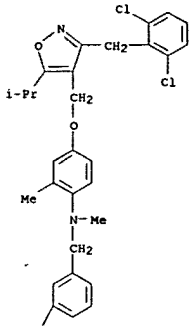

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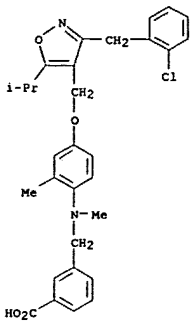
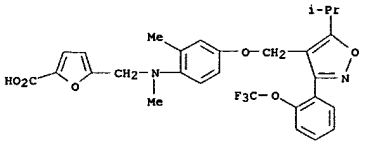
RN 700834-93-1 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-[(2-chlorophenyl)methyl]-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]methyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 700834-95-3 CAPLUS
CN 2-Furancarboxylic acid, 5-[(methyl[2-methyl-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]amino]methyl]- (9CI)
(CA INDEX NAME)



RN 700834-96-4 CAPLUS
CN Benzoic acid, 4-[(methyl[2-methyl-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]amino]methyl]- (9CI)
(CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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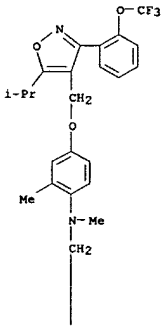

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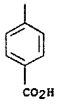

RN 700834-97-5 CAPLUS
CN Benzoic acid, 3-[(methyl[2-methyl-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]amino]methyl]- (9CI)
(CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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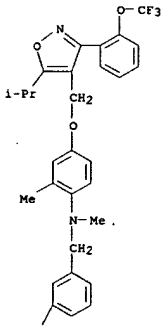

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RN 700834-98-6 CAPLUS
CN 2-Furancarboxylic acid, 5-[(methyl[2-methyl-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]amino]methyl]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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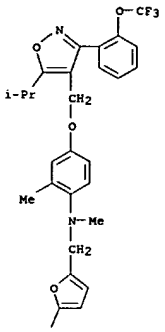

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RN 700834-99-7 CAPLUS
CN Benzoic acid, 4-[[methyl[2-methyl-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]amino]methyl]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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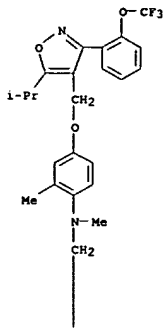

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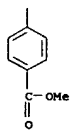

RN 700835-00-3 CAPLUS
CN Benzoic acid, 4-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]amino]carbonyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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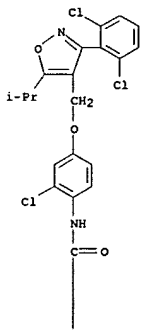

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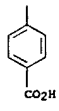

RN 700835-01-4 CAPLUS
CN Benzoic acid, 3-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]amino]carbonyl]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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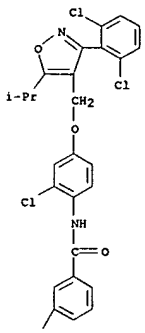

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RN 700835-03-6 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]amino]carbonyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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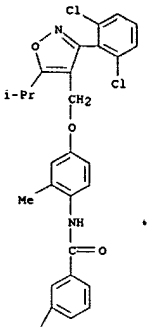

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RN 700835-04-7 CAPLUS
CN Benzoic acid, 4-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]amino]carbonyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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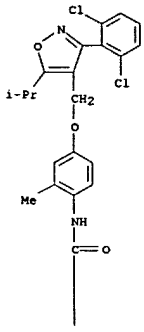

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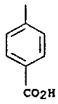

RN 700835-05-8 CAPLUS
CN Benzoic acid, 3-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]amino]carbonyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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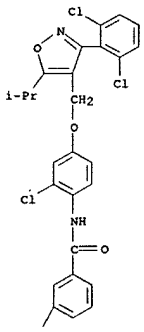

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RN 700835-06-9 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]carbonyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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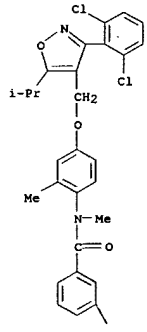

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RN 700835-07-0 CAPLUS
CN Benzoic acid, 3-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]methylamino]carbonyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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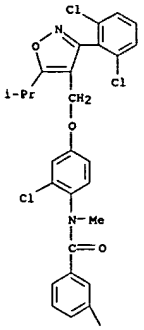

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L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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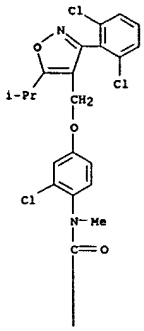

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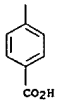

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CN Benzoic acid, 3-[[methyl[2-methyl-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]amino]carbonyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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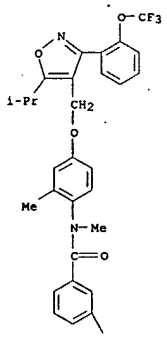

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RN 700835-10-5 CAPLUS
CN Benzoic acid, 3-[[[2-methyl-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]amino]carbonyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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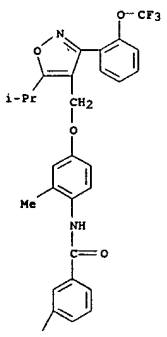

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RN 700835-11-6 CAPLUS
CN Benzoic acid, 3-[[[2-chloro-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]methylamino]carbonyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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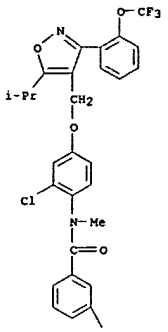

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RN 700835-12-7 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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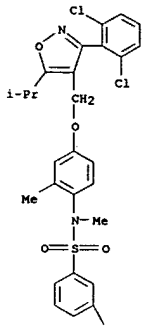

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RN 700835-13-8 CAPLUS
CN Benzoic acid, 3-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]amino]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)

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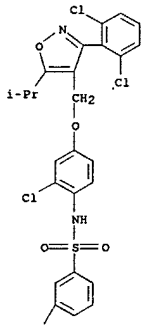

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CN Benzoic acid, 3-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]amino]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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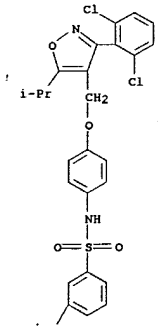

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RN 700835-16-1 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]amino]sulfonyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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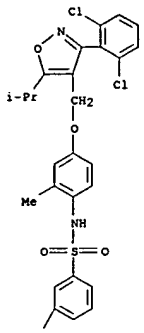

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RN 700835-17-2 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]amino]sulfonyl]- (9CI) (CA INDEX NAME)

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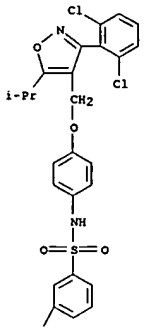

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RN 700835-18-3 CAPLUS
CN Benzoic acid, 3-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]methylamino]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)

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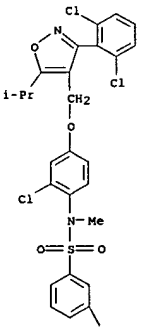

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RN 700835-19-4 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]methylamino]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)

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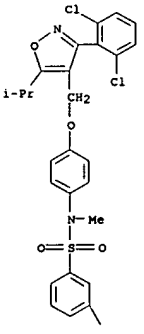

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RN 700835-20-7 CAPLUS
CN Benzoic acid, 3-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethylamino]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)

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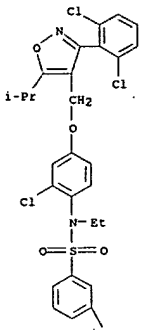

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RN 700835-21-8 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]ethylamino]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)

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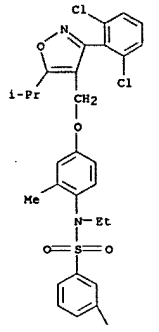

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RN 700835-22-9 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethylamino]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)

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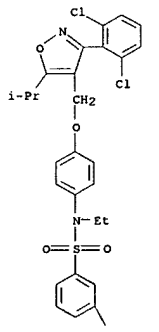

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RN 700835-23-0 CAPLUS
CN Benzoic acid, 3-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]amino]sulfonyl]- (9CI) (CA INDEX NAME)

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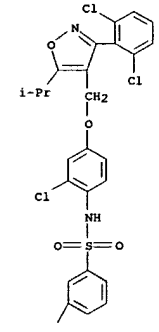

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RN 700835-24-1 CAPLUS
CN Benzoic acid, 3-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]methylamino]sulfonyl]- (9CI) (CA INDEX NAME)

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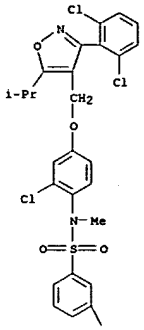

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RN 700835-25-2 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]sulfonyl]- (9CI) (CA INDEX NAME)

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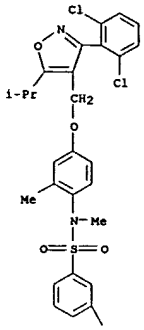

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RN 700835-26-3 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]methylamino]sulfonyl]- (9CI) (CA INDEX NAME)

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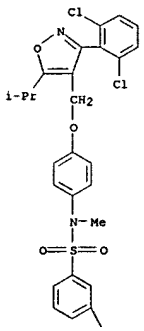

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RN 700835-27-4 CAPLUS
CN Benzoic acid, 3-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethylamino]sulfonyl]- (9CI) (CA INDEX NAME)

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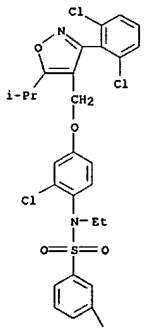

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RN 700835-28-5 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]ethylamino]sulfonyl]- (9CI) (CA INDEX NAME)

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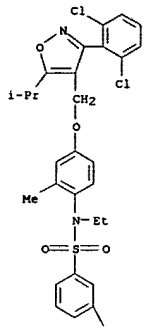

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RN 700835-29-6 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethylamino]sulfonyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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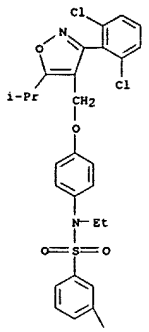

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RN 700835-30-9 CAPLUS
CN Benzoic acid, 4-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]amino]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)

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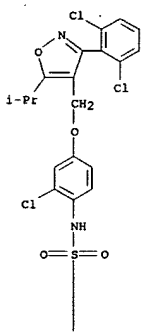

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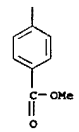

RN 700835-31-0 CAPLUS
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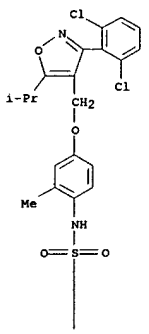

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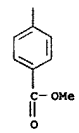

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CN Benzoic acid, 4-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]amino]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)

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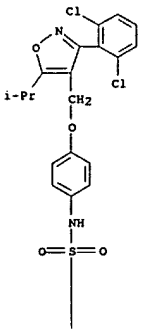

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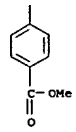

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CN Benzoic acid, 4-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]amino]sulfonyl]- (9CI) (CA INDEX NAME)

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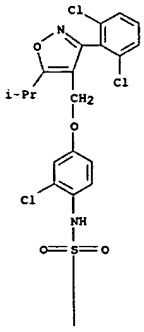

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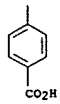

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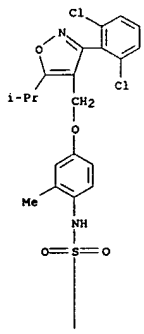

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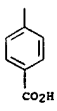

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CN Benzoic acid, 4-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]amino]sulfonyl]- (9CI) (CA INDEX NAME)

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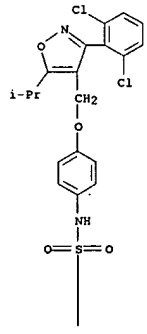

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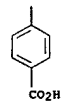

RN 700835-36-5 CAPLUS
CN Benzoic acid, 4-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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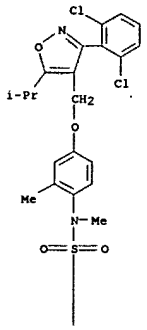

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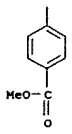

RN 700835-37-6 CAPLUS
CN Benzoic acid, 4-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]methylamino]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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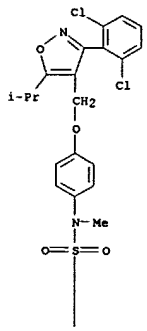

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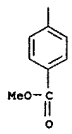

RN 700835-38-7 CAPLUS
CN Benzoic acid, 4-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethylamino]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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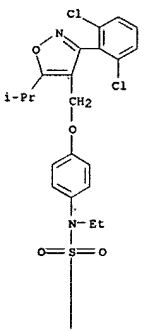

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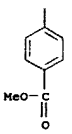

RN 700835-39-8 CAPLUS
CN Benzoic acid, 4-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]methylamino]sulfonyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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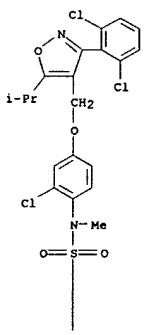

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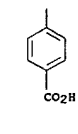

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CN Benzoic acid, 4-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]sulfonyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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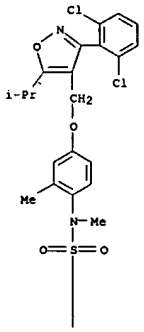

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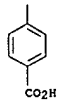

RN 700835-41-2 CAPLUS
CN Benzoic acid, 4-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]methylamino]sulfonyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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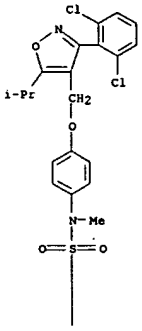

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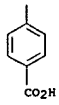

RN 700835-42-3 CAPLUS
CN Benzoic acid, 4-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethylamino]sulfonyl]- (9CI) (CA INDEX NAME)

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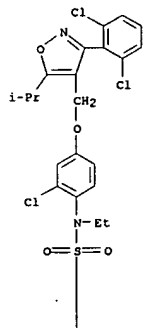

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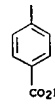

RN 700835-43-4 CAPLUS
CN Benzoic acid, 4-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]ethylamino]sulfonyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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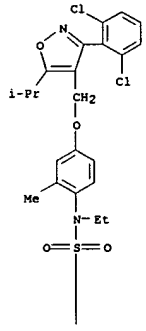

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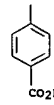

RN 700835-44-5 CAPLUS
CN Benzoic acid, 4-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethylamino]sulfonyl]- (9CI) (CA INDEX NAME)

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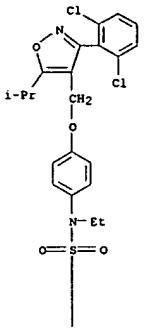

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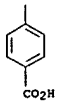

RN 700835-45-6 CAPLUS
CN Benzoic acid, 3-[[[2-chloro-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]amino]sulfonyl]-(9CI) (CA INDEX NAME)

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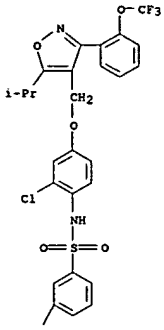

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RN 700835-46-7 CAPLUS
CN Benzoic acid, 3-[[[2-methyl-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]amino]sulfonyl]-(9CI) (CA INDEX NAME)

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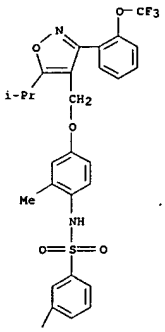

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RN 700835-47-8 CAPLUS
CN Benzoic acid, 3-[[[2-chloro-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]methylamino]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)

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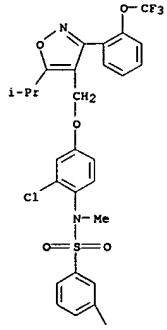

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RN 700835-48-9 CAPLUS
CN Benzoic acid, 3-[[methyl[2-methyl-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]amino]sulfonyl]-, methyl ester (9CI) (CA INDEX NAME)

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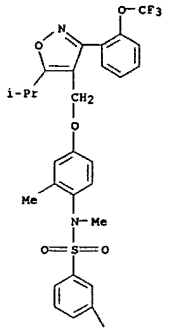

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RN 700835-49-0 CAPLUS
CN Benzoic acid, 3-[[[2-chloro-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]methylamino]sulfonyl]- (9CI) (CA INDEX NAME)

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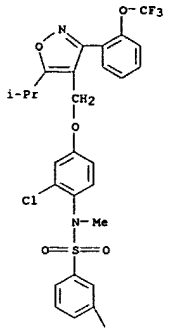

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RN 700835-50-3 CAPLUS
CN Benzoic acid, 3-[[methyl[2-methyl-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]amino]sulfonyl]- (9CI) (CA INDEX NAME)

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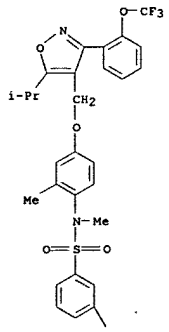

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RN 700835-51-4 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-[(2,6-dichlorophenyl)methyl]-5-ethyl-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]sulfonyl]- (9CI) (CA INDEX NAME)

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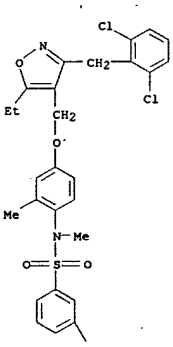

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RN 700835-52-5 CAPLUS
CN Benzoic acid, 4-[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]methoxy]-, methyl ester (9CI) (CA INDEX NAME)

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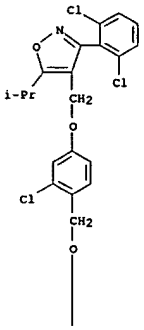

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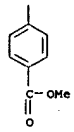

RN 700835-53-6 CAPLUS
CN Benzoic acid,
3-[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]methoxy]-, methyl ester (9CI) (CA INDEX NAME)

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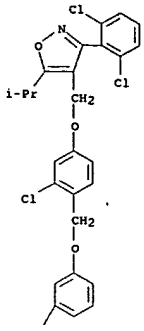

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RN 700835-54-7 CAPLUS
CN Benzoic acid,
3-[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]methoxy]- (9CI) (CA INDEX NAME)

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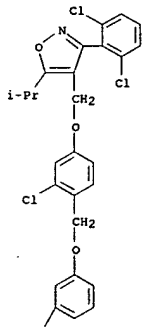

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RN 700835-55-8 CAPLUS
CN Benzoic acid,
3-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]methyl]thio]- (9CI) (CA INDEX NAME)

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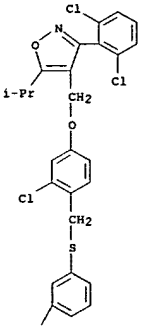

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RN 700835-56-9 CAPLUS
CN Benzoic acid, 3-[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methoxy]- (9CI) (CA INDEX NAME)

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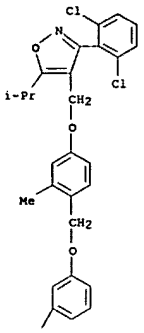

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RN 700835-57-0 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methyl]thio]- (9CI) (CA INDEX NAME)

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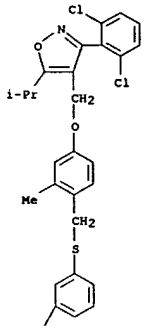

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RN 700835-58-1 CAPLUS
CN Benzoic acid, 4-[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]methoxy]- (9CI) (CA INDEX NAME)

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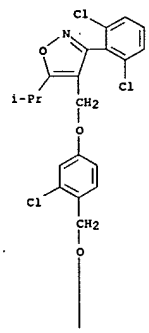

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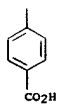

RN 700835-59-2 CAPLUS
CN Benzoic acid, 4-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]methyl]thio]- (9CI) (CA INDEX NAME)

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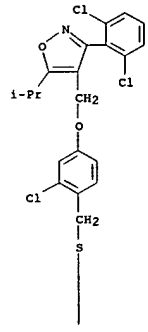

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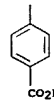

RN 700835-60-5 CAPLUS
CN Benzoic acid, 3-[[2-chloro-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]methoxy]-, methyl ester (9CI) (CA INDEX NAME)

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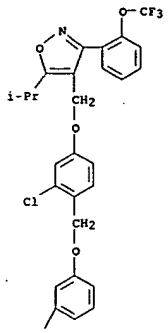

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RN 700835-61-6 CAPLUS
CN Benzoic acid, 3-[[2-methyl-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]methoxy]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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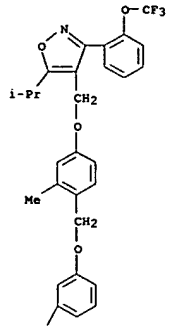

PAGE 2-A

RN 700835-62-7 CAPLUS
CN Benzoic acid, 3-[[2-chloro-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]methoxy]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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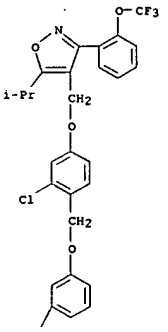

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RN 700835-63-8 CAPLUS
CN Benzoic acid, 3-[[2-methyl-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]methoxy]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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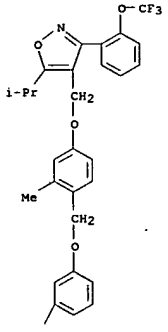

PAGE 2-A

RN 700835-64-9 CAPLUS
CN Benzoic acid, 3-[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-ethyl-4-isoxazolyl]methoxy]phenyl]methoxy]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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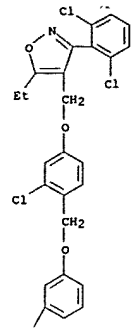

PAGE 2-A

RN 700835-65-0 CAPLUS
CN Benzoic acid, 3-[[[2-chloro-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]methyl]thio]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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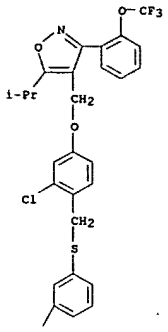

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RN 700835-66-1 CAPLUS
CN Benzoic acid, 3-[[[2-methyl-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]methyl]thio]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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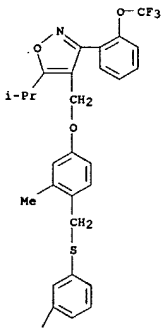

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RN 700835-67-2 CAPLUS
CN Benzoic acid, 3-[[[2-chloro-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]methyl]thio]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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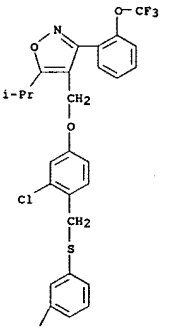

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RN 700835-68-3 CAPLUS
CN Benzoic acid, 3-[[[2-methyl-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]methyl]thio]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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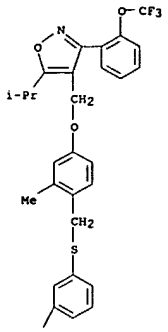

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RN 700835-69-4 CAPLUS
CN Benzoic acid,
3-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]methyl]methylamino]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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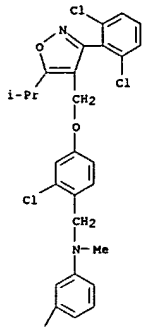

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RN 700835-70-7 CAPLUS
CN Benzoic acid,
3-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]methyl]methylamino]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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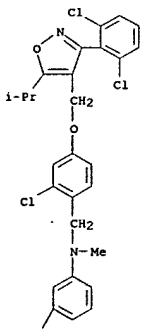

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RN 700835-71-8 CAPLUS
CN Benzoic acid,
3-[[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]methyl]amino]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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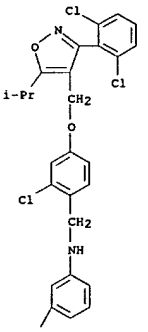

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RN 700835-72-9 CAPLUS
CN Benzoic acid, 3-[[[2-chloro-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]methyl]amino]-, ethyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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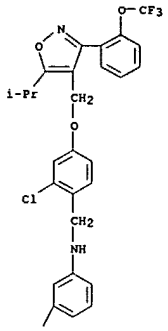

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RN 700835-73-0 CAPLUS
CN Benzoic acid, 3-[[[2-chloro-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]methyl]amino]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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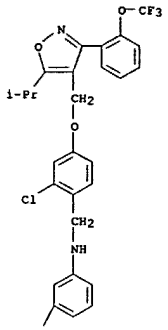

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RN 700835-74-1 CAPLUS
CN Benzoic acid, 3-[[[2-chloro-4-[[5-(1-methylethyl)-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]methyl]methylamino]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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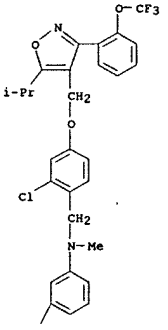

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RN 700835-75-2 CAPLUS
CN Benzoic acid, 4-[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenoxy]methyl]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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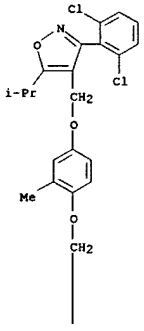

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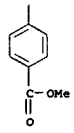

RN 700835-76-3 CAPLUS
CN Benzoic acid, 3-[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenoxy]methyl]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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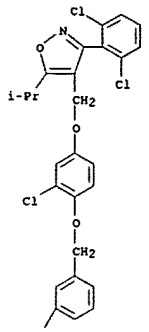

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RN 700835-77-4 CAPLUS
CN Benzoic acid, 3-[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenoxy]methyl]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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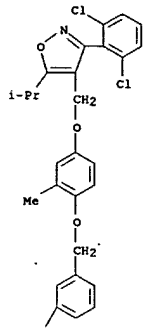

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RN 700835-78-5 CAPLUS
CN Benzoic acid, 3-[[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenoxy]methyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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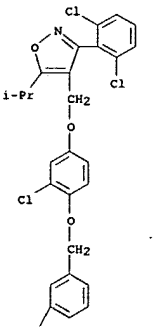

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RN 700835-79-6 CAPLUS
CN Benzoic acid, 3-[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenoxy]methyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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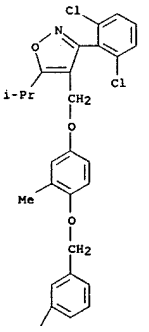

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RN 700835-80-9 CAPLUS
CN Benzoic acid, 4-[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenoxy]methyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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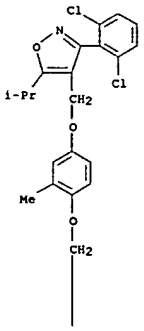

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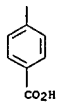

RN 700836-32-4 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-(2,6-dichlorophenyl)-5-ethyl-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]methyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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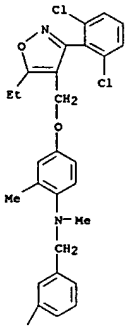

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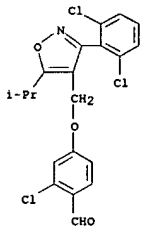
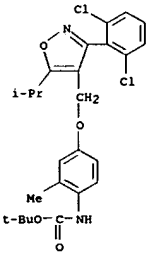
IT 278597-32-3P 700835-82-1P 700835-83-2P
700835-84-3P 700835-85-4P 700835-86-5P
700835-87-6P 700835-88-7P 700835-89-8P
700835-90-1P 700835-91-2P 700835-92-3P
700835-93-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(Preparation of isoxazole derivs. as farnesoid x receptor agonists)

RN 278597-32-3 CAPLUS
CN Benzaldehyde, 2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

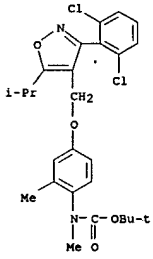


RN 700835-82-1 CAPLUS
CN Carbamic acid, [4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

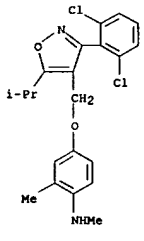


RN 700835-83-2 CAPLUS
CN Carbamic acid, [4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methyl-, 1,1-dimethylethyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 700835-84-3 CAPLUS
CN Benzenamine, 4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-N,2-dimethyl- (9CI) (CA INDEX NAME)



RN 700835-85-4 CAPLUS
CN Benzoic acid, 3-[[[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]methylamino]methyl]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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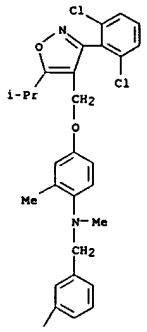

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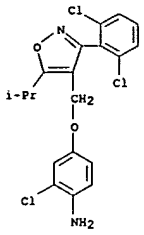
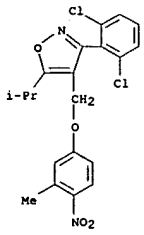
RN 700835-86-5 CAPLUS
CN Benzenamine, 2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

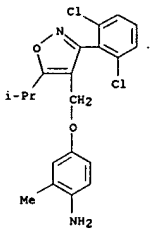


RN 700835-87-6 CAPLUS
CN Isoxazole, 3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-[(3-methyl-4-nitrophenoxy)methyl]- (9CI) (CA INDEX NAME)

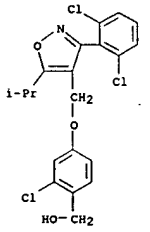


RN 700835-88-7 CAPLUS
CN Benzenamine, 4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methyl- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

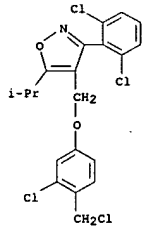


RN 700835-89-8 CAPLUS
CN Benzenemethanol, 2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]- (9CI) (CA INDEX NAME)

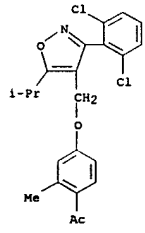


RN 700835-90-1 CAPLUS
CN Isoxazole, 4-[[3-chloro-4-(chloromethyl)phenoxy]methyl]-3-(2,6-dichlorophenyl)-5-(1-methylethyl)- (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

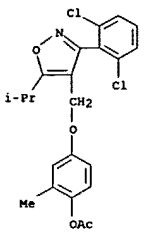


RN 700835-91-2 CAPLUS
CN Ethanone, 1-[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]- (9CI) (CA INDEX NAME)

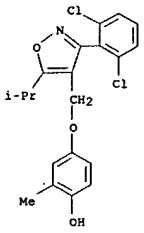


RN 700835-92-3 CAPLUS
CN Phenol, 4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methyl-, acetate (ester) (9CI) (CA INDEX NAME)

L3 ANSWER 28 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 700835-93-4 CAPLUS
CN Phenol,
4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-
2-methyl- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

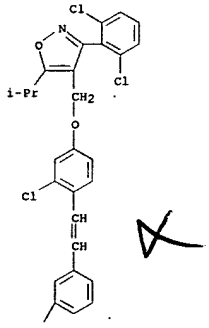
L3 ANSWER 29 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:453343 CAPLUS
DOCUMENT NUMBER: 141:19434
TITLE: Crystal structure of the human farnesoid X receptor ligand binding domain complexed with fexaramine and identification and development of novel small molecule ligands for FXR
INVENTOR(S): Downes, Michael R.; Verdicia, Mark A.; Noel, Joseph P.; Evans, Ronald M.; Bowman, Lindsey J.; Bowman, Marianne
PATENT ASSIGNEE(S): The Salk Institute for Biological Studies, USA
SOURCE: PCT Int. Appl., 139 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004046323	A2	20040603	WO 2003-US36548	20031114
WO 2004046323	A3	20041209		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW: BW, GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003298654	A1	20040615	AU 2003-298654	20031114
US 2006194949	A1	20060831	US 2006-535042	20060109
PRIORITY APPLN. INFO.:			US 2002-426665P	P 20021115
			US 2002-426668P	P 20021115
			WO 2003-US36548	W 20031114

AB The present invention provides compns. comprising the ligand binding domain (LBD) of a human farnesoid X receptor (FXR) in crystalline form. In alternative embodiments, the LBD of FXR is complexed with a ligand therefor. There are provided high resolution structures and structure coordinates of FXR complexed with a novel high affinity agonist, fexaramine. The discovered structure of a FXR LBD provides the first three-dimensional view of the structural basis for FXR ligand binding. The present invention further provides a computer for producing a three-dimensional representation of FXR or a complex thereof, and a computer for determining at least a portion of the structure coordinates of FXR or a complex thereof. The present invention further provides methods of using this structural information to predict mols. capable of binding to

L3 ANSWER 29 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
FXR; to identify compds. with agonist, antagonist or partial agonist activity for FXR; and to det. whether a test compd. is capable of binding to the LBD of FXR. The present invention further provides compns. comprising compds. identified by such invention methods. Identification and development of novel small mol. ligands for FXR, and activation of FXR and induction of FXR target genes by these novel compds. is disclosed.
IT 278779-30-9P, GW4064
RL: BSU (Biological study, unclassified); CPN (Combinatorial preparation); THU (Therapeutic use); BIOL (Biological study); CMBI (Combinatorial study); PREP (Preparation); USES (Uses)
(FXR ligand; crystal structure of human farnesoid X receptor ligand binding domain complexed with fexaramine and identification and development of novel small mol. ligands for FXR)
RN 278779-30-9 CAPLUS
CN Benzoic acid,
3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

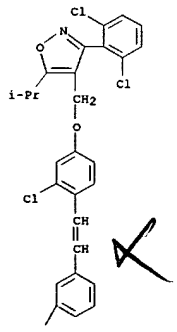
PAGE 1-A



PAGE 2-A

L3 ANSWER 30 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2004:12695 CAPLUS
DOCUMENT NUMBER: 140:416971
TITLE: Influence of genomics on structure-based drug design
AUTHOR(S): Wang, Baolei; Li, Zhengming; Zang, Hongjun
CORPORATE SOURCE: State Key Laboratory of Elemento-organic Chemistry, Institute of Elemento-organic Chemistry, Nankai University, Tianjin, 300071, Peop. Rep. China
SOURCE: Huaxue Jinzhan (2003), 15(6), 505-511
CODEN: HJINEL; ISSN: 1005-281X
PUBLISHER: Huaxue Jinzhan Bianjibu
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Chinese
AB A review. Drug design has been relied on target enzyme which usually is a protein mol. In recent years, with the successful progress of Human Genome Project, genomics shows increasing influence on drug design. In this paper, such influence is reviewed from the progress of structural genomics, chemical genomics and microbial genomics.
IT 278779-30-9, GW 4064 291521-35-2, GW 9047
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(influence of genomics on structure-based drug design)
RN 278779-30-9 CAPLUS
CN Benzoic acid,
3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A

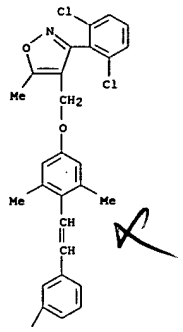


L3 ANSWER 30 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 2-A

RN 291521-35-2 CAPLUS
CN Benzoic acid, 3-[2-[4-[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]methoxy]-2,6-dimethylphenyl]ethenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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L3 ANSWER 31 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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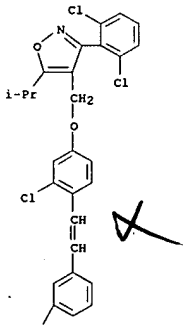

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REFERENCE COUNT: 53 THERE ARE 53 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 31 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:973413 CAPLUS
DOCUMENT NUMBER: 140:229012
TITLE: Hepatoprotection by the farnesoid X receptor agonist GW4064 in rat models of intra- and extrahepatic cholestasis
AUTHOR(S): Liu, Yaping; Binz, Jane; Numerick, Mary Jo; Dennis, Steve; Luo, Guizhen; Desai, Bhasha; MacKenzie, Kathleen I.; Hansfield, Traci A.; Kliewer, Steven A.; Goodwin, Bryan; Jones, Stacey A.
CORPORATE SOURCE: Nuclear Receptor Functional Analysis, High Throughput Biology, GlaxoSmithKline, Research Triangle Park, NC, USA
SOURCE: Journal of Clinical Investigation (2003), 112(11), 1678-1687
CODEN: JCINAO; ISSN: 0021-9738
PUBLISHER: American Society for Clinical Investigation
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Farnesoid X receptor (FXR) is a bile acid-activated transcription factor that is a member of the nuclear hormone receptor superfamily. Fxr-null mice exhibit a phenotype similar to Byler disease, an inherited cholestatic liver disorder. In the liver, activation of FXR induces transcription of transporter genes involved in promoting bile acid clearance and represses genes involved in bile acid biosynthesis. We investigated whether the synthetic FXR agonist GW4064 could protect against cholestatic liver damage in rat models of extrahepatic and intrahepatic cholestasis. In the bile duct-ligation and α-naphthylisothiocyanate models of cholestasis, GW4064 treatment resulted in significant redns. in serum alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase, as well as other markers of liver damage. Rats that received GW4064 treatment also had decreased incidence and extent of necrosis, decreased inflammatory cell infiltration, and decreased bile duct proliferation. Anal. of gene expression in livers from GW4064-treated cholestatic rats revealed decreased expression of bile acid biosynthetic genes and increased expression of genes involved in bile acid transport, including the phospholipid flippase MDR2. The hepatoprotection seen in these animal models by the synthetic FXR agonist suggests FXR agonists may be useful in the treatment of cholestatic liver disease.

IT 278779-30-9, GW4064
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(hepatoprotection by farnesoid X receptor agonist GW4064 in rat models of intra- and extrahepatic cholestasis)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 32 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:855658 CAPLUS
DOCUMENT NUMBER: 139:317457
TITLE: Compositions and methods using farnesoid X receptor ligands for hepatoprotection and treatment of cholestasis
INVENTOR(S): Kliewer, Steven Anthony; Willson, Timothy Mark
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA
SOURCE: U.S. Pat. Appl. Publ., 8 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003203939	A1	20031030	US 2002-132311	20020425
US 6987121	B2	20060117		
WO 2003090745	A1	20031106	WO 2003-US10519	20030407
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2003226283	A1	20031110	AU 2003-226283	20030407
EP 1501506	A1	20050202	EP 2003-747270	20030407
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, SK				

PRIORITY APPLN. INFO.: US 2002-132311 A 20020425
WO 2003-US10519 W 20030407

OTHER SOURCE(S): MARPAT 139:317457

AB Methods for the treatment of cholestatic liver disease and reduction and prevention of hepatic injury resulting from cholestasis via administration of a FXR ligand are provided. Bile duct-ligated rats treated with FXR ligand GW4064 had a pronounced improvement in liver function as defined by a reduction in a panel of liver disease serum marker enzymes.

IT 278779-30-9, GW4064
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(FXR agonist; farnesoid X receptor ligands for hepatoprotection and treatment of cholestasis)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 32 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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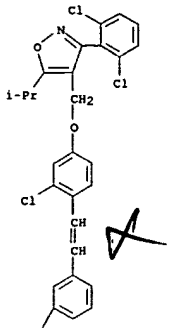

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REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L3 ANSWER 33 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:777952 CAPLUS
DOCUMENT NUMBER: 139:286360
TITLE: Methods using farnesoid X receptor (FXR) agonists for weight loss and alteration of cell metabolism
INVENTOR(S): Jones, Stacey Ann; Kliewer, Steven Anthony; Mansfield,
Traci Ann
PATENT ASSIGNEE(S): Smithkline Beecham Corporation, USA; Curagen Corporation
SOURCE: PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003080803	A2	20031002	WO 2003-US8634	20030319
WO 2003080803	A3	20041021		
W:	AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW			
RW:	GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG			
AU 2003225903	A1	20031008	AU 2003-225903	20030319
US 2005107475	A1	20050519	US 2003-507082	20030319
PRIORITY APPLN. INFO.:			US 2002-366463P	P 20020321
			WO 2003-US8634	W 20030319

OTHER SOURCE(S): MARPAT 139:286360
AB Treatment of human hepatocytes with farnesoid X receptor (FXR) agonists resulted in increased expression of FGF-19. Methods of using FXR agonists
to alter cell metabolism, and in pharmaceutical weight loss methods, are described.
IT 278779-30-9, GW4064 278779-30-9D, GW4064, amino acid conjugates
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(farnesoid X receptor agonists for weight loss and alteration of cell metabolism)
RN 278779-30-9 CAPLUS
CN Benzoic acid,
3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 33 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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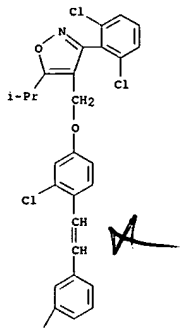

PAGE 2-A

RN 278779-30-9 CAPLUS
CN Benzoic acid,
3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 33 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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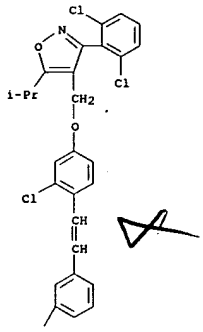
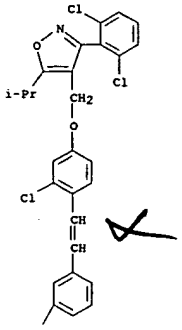


PAGE 2-A

L3 ANSWER 34 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:723027 CAPLUS
DOCUMENT NUMBER: 139:286515
TITLE: Estrogen receptor α regulates expression of the orphan receptor small heterodimer partner
AUTHOR(S): Lai, KehDih; Harnish, Douglas C.; Evans, Mark J.
CORPORATE SOURCE: Wyeth Research, Collegeville, PA, 19426, USA
SOURCE: Journal of Biological Chemistry (2003), 278(38), 36418-36429
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Hormonal status can influence diverse metabolic pathways. Small heterodimer partner (SHP) is an orphan nuclear receptor that can modulate the activity of several transcription factors. Estrogens are here shown to directly induce expression of the SHP in the mouse and rat liver and in human HepG2 cells. SHP is rapidly induced within 2 h following treatment of mice with ethynylestradiol (EE) or the estrogen receptor α (ERα)-selective compound Pr pyrazole triol (PPT). SHP induction by these estrogens is completely absent in ERαKO mice. Mutation of the human SHP promoter defined HNF-3, HNF-4, GATA, and AP-1 sites as important for basal activity, whereas EE induction required two distinct elements located between -309 and -267. One of these elements contains an estrogen response element half-site that bound purified ERα, and ERα with a mutated DNA binding domain was unable to stimulate SHP promoter activity. This ERα binding site overlaps the known farnesoid X receptor (FXR) binding site in the SHP promoter, and the combination of EE plus FXR agonists did not produce an additive induction of SHP expression in mice. Surprisingly, induction of SHP by EE did not inhibit expression of the known SHP target genes cholesterol 7α-hydroxylase (CYP7A1) or sterol 12α-hydroxylase (CYP8B1). However, the direct regulation of SHP expression may provide a basis for some of the numerous biol. effects of estrogens.
IT 278779-30-9, GW4064
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(estrogen receptor α regulates expression of orphan receptor small heterodimer partner as studied in mouse and rat liver and in human HepG2 cells)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 34 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



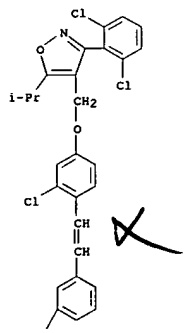
PAGE 2-A

REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 35 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:698404 CAPLUS
DOCUMENT NUMBER: 140:87450
TITLE: Farnesoid X receptor agonists suppress hepatic apolipoprotein CIII expression
AUTHOR(S): Claudel, Thierry; Inoue, Yusuke; Barbier, Olivier; Duran-Sandoval, Daniel; Kosykh, Vladimir; Fruchart, Jamila; Fruchart, Jean-Charles; Gonzalez, Frank J.; Staels, Bart
CORPORATE SOURCE: Departement d'Atherosclerose, UR545 INSERM, Institut Pasteur de Lille, Lille, Fr.
SOURCE: Gastroenterology (2003), 125(2), 544-555
CODEN: GASTAB; ISSN: 0016-5085
PUBLISHER: W. B. Saunders Co.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background & Aims: Increased serum triglyceride levels constitute a risk factor for coronary heart disease. Apolipoprotein CIII (Apo CIII) is a determinant of serum triglyceride metabolism In this study, we investigated whether activators of the nuclear farnesoid X receptor (FXR) modulate Apo CIII gene expression. Methods: The influence of bile acids and synthetic FXR activators on Apo CIII and triglyceride metabolism was studied in vivo by using FXR wild-type and FXR-deficient mice and in vitro by using human primary hepatocytes and HepG2 cells. Results: In mice, treatment with the FXR agonist taurocholic acid strongly decreased serum triglyceride levels, an effect associated with reduced Apo CIII serum and liver mRNA levels. By contrast, no change was observed in FXR-deficient mice. Incubation of human primary hepatocytes and HepG2 cells with bile acids or the nonsteroidal synthetic FXR agonist GW4064 resulted in a dose-dependent downregulation of Apo CIII gene expression. Promoter transfection expts. and mutation anal. showed that bile acid-activated FXR decrease human Apo CIII promoter activity via a neg. FXR response element located in the 14 footprint between nucleotides -739 and -704. Chromatin immunopptn. expts. showed that bile acid treatment led to binding of FXR/retinoid X receptor heterodimers to and displacement of HNF4α from this site. Bile acid treatment still repressed liver Apo CIII gene expression in hepatic HNF4α-deficient mice, suggesting an active rather than a competitive mechanism of Apo CIII repression by the FXR. Conclusions: We identified bile acid and synthetic activators of the nuclear FXR as neg. regulators of Apo CIII expression, an effect that may contribute to the triglyceride-decreasing action of FXR agonists.
IT 278779-30-9, GW4064
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(farnesoid X receptor agonists suppress hepatic apolipoprotein CIII expression)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 35 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



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REFERENCE COUNT: 71 THERE ARE 71 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

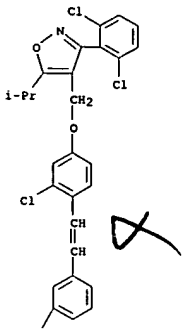
L3 ANSWER 36 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:579493 CAPLUS
DOCUMENT NUMBER: 139:256039
TITLE: Human kininogen gene is transactivated by the farnesoid X receptor
AUTHOR(S): Zhao, Annie; Lew, Jane-L.; Huang, Li; Yu, Jinghua; Zhang, Theresa; Hrywna, Yaroslav; Thompson, John R.; de Pedro, Nuria; Blevins, Richard A.; Pelaez, Fernando; Wright, Samuel D.; Cui, Jisong
CORPORATE SOURCE: Departments of Atherosclerosis and Endocrinology, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Journal of Biological Chemistry (2003), 278(31), 28765-28770
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Human kininogen belongs to the plasma kallikrein-kinin system. High mol. weight kininogen is the precursor for two-chain kinin-free kininogen and bradykinin. It has been shown that the two-chain kinin-free kininogen has the properties of anti-adhesion, anti-platelet aggregation, and anti-thrombosis, whereas bradykinin is a potent vasodilator and mediator of inflammation. In this study the human kininogen gene is strongly up-regulated by agonists of the farnesoid X receptor (FXR), a nuclear receptor for bile acids. In primary human hepatocytes, both the endogenous FXR agonist chenodeoxycholate and synthetic FXR agonist GW4064 increased kininogen mRNA with a maximum induction of 8-10-fold. A more robust induction of kininogen expression was observed in HepG2 cells, where kininogen mRNA was increased by chenodeoxycholate or GW4064 up to 130-140-fold as shown by real time PCR. Northern blot anal. confirmed the up-regulation of kininogen expression by FXR agonists. To determine whether kininogen is a direct target of FXR, the authors examined the sequence of the kininogen promoter and identified a highly conserved FXR response element (inverted repeat, IR-1) in the proximity of the kininogen promoter (-66/-54). FXR/RXRα heterodimers specifically bind to this IR-1. A construct of a minimal promoter with the luciferase reporter containing this IR-1 was transactivated by FXR. Deletion or mutation of this IR-1 abolished FXR-mediated promoter activation, indicating that this IR-1 element is responsible for the promoter transactivation by FXR. The authors conclude that kininogen is a novel and direct target of FXR, and bile acids may play a role in the vasodilation and anti-coagulation processes.

IT 278779-30-9, GW4064
RL: BSU (Biological study, unclassified); BIOL (Biological study) (human kininogen gene is transactivated by the farnesoid X receptor in primary human hepatocytes)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-

L3 ANSWER 36 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

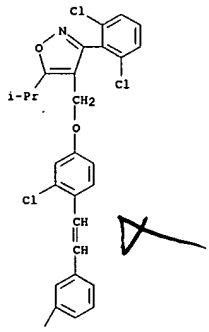
L3 ANSWER 37 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:375244 CAPLUS
DOCUMENT NUMBER: 139:159454
TITLE: A chemical, genetic, and structural analysis of the nuclear bile acid receptor FXR
AUTHOR(S): Downes, Michael; Verdecia, Mark A.; Roecker, A. J.; Hughes, Robert; Hogenesch, John B.; Kast-Woelbern, Heidi R.; Bowman, Marianne E.; Ferrer, Jean-Luc; Anisfeld, Andrew M.; Edwards, Peter A.; Rosenfeld, John M.; Alvarez, Jacqueline G. A.; Noel, Joseph P.; Nicolaou, K. C.; Evans, Ronald M.
CORPORATE SOURCE: Gene Expression Laboratory, Howard Hughes Medical Institute, La Jolla, CA, 92037, USA
SOURCE: Molecular Cell (2003), 11(4), 1079-1092
CODEN: MOCEFL; ISSN: 1097-2765
PUBLISHER: Cell Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The farnesoid X receptor (FXR) functions as a bile acid (BA) sensor coordinating cholesterol metabolism, lipid homeostasis, and absorption of dietary fats and vitamins. However, BAs are poor reagents for characterizing FXR functions due to multiple receptor independent properties. Accordingly, using combinatorial chemical we evolved a small mol. agonist termed fexaramine with 100-fold increased affinity relative to natural compds. Gene-profiling expts. conducted in hepatocytes with FXR-specific fexaramine vs. the primary BA chenodeoxycholic acid (CDCA) produced remarkably distinct genomic targets. Highly diffracting cocrystals (1.78 Å) of fexaramine bound to the ligand binding domain of FXR revealed the agonist sequestered in a 726 Å3 hydrophobic cavity and suggest a mechanistic basis for the initial step in the BA signaling pathway. The discovery of fexaramine will allow us to unravel the FXR genetic network from the BA network and selectively manipulate components of the cholesterol pathway that may be useful in treating cholesterol-related human diseases.

IT 278779-30-9, GW 4064
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses) (chemical, genetic, and structural anal. of nuclear bile acid receptor FXR)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 37 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



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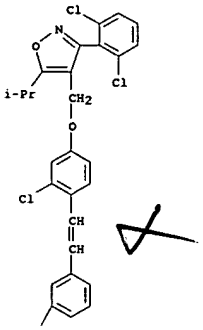
REFERENCE COUNT: 39 THERE ARE 39 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 38 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:237176 CAPLUS
DOCUMENT NUMBER: 139:17879
TITLE: Differential regulation of rat and human CYP7A1 by the nuclear oxysterol receptor liver X receptor-α
AUTHOR(S): Goodwin, Bryan; Watson, Michael A.; Kim, Hwajin; Miao, Ji; Kemper, Jongsook Kim; Kliewer, Steven A.
CORPORATE SOURCE: Nuclear Receptor Discovery Research, GlaxoSmithKline Research and Development, Research Triangle Park, NC, 27709, USA
SOURCE: Molecular Endocrinology (2003), 17(3), 386-394
CODEN: MOENEN; ISSN: 0888-8809
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB In rodent liver, transcription of the gene encoding cholesterol 7α-hydroxylase (CYP7A1), which catalyzes the rate-limiting step in the classic bile acid synthetic pathway, is stimulated by the liver X receptor α (LXRα), a nuclear receptor for oxysterol metabolites of cholesterol. This feed-forward regulatory loop provides a mechanism for the elimination of excess cholesterol from the body. The authors demonstrate that in primary cultures of human hepatocytes, activation of LXRα has the opposite effect, repressing CYP7A1 expression. This repression is mediated, at least in part, through induction of the orphan nuclear receptor, short heterodimer partner (SHP), which is also induced by bile acids. The authors demonstrate that SHP is regulated directly by LXRα through a DNA response element that overlaps with the previously characterized bile acid response element. The authors' data reveal a fundamental difference in the regulation of CYP7A1 in rodent and human hepatocytes and provide evidence that different species employ distinct mol. strategies to regulate cholesterol homeostasis.
IT 278779-30-9, GW4064
RL: BSU (Biological study, unclassified); BIOL (Biological study) (differential regulation of rat and human CYP7A1 by nuclear oxysterol receptor liver X receptor-α)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 38 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



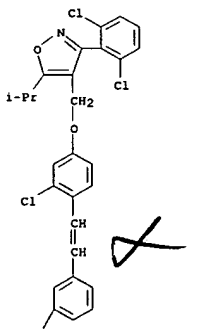
PAGE 2-A

REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 39 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:204786 CAPLUS
DOCUMENT NUMBER: 139:79298
TITLE: Guggulsterone Is a Farnesoid X Receptor Antagonist in Coactivator Association Assays but Acts to Enhance Transcription of Bile Salt Export Pump
AUTHOR(S): Cui, Jisong; Huang, Li; Zhao, Annie; Lew, Jane-L.; Yu, Jinghua; Sahoo, Soumya; Meinke, Peter T.; Royo, Inmaculada; Pelaez, Fernando; Wright, Samuel D.
CORPORATE SOURCE: Department of Atherosclerosis and Endocrinology, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Journal of Biological Chemistry (2003), 278(12), 10214-10220
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Guggulipid is an extract of the guggul tree Commiphora mukul and has been widely used to treat hyperlipidemia in humans. The plant sterol guggulsterone (GS) is the active agent in this extract Recent studies have shown that GS can act as an antagonist ligand for farnesoid X receptor (FXR) and decrease expression of bile acid-activated genes. Here we show that GS, although an FXR antagonist in coactivator association assays, enhances FXR agonist-induced transcription of bile salt export pump (BSEP), a major hepatic bile acid transporter. In HepG2 cells, in the presence of an FXR agonist such as chenodeoxycholate or GW4064, GS enhanced endogenous BSEP expression with a maximum induction of 400-500% that induced by an FXR agonist alone. This enhancement was also readily observed in FXR-dependent BSEP promoter activation using a luciferase reporter construct. In addition, GS alone slightly increased BSEP promoter activation in the absence of an FXR agonist. Consistent with the results in HepG2, guggulipid treatment in Fisher rats increased BSEP mRNA. Interestingly, in these animals expression of the orphan nuclear receptor SHP (small heterodimer partner), a known FXR target, was also significantly increased, whereas expression of other FXR targets including cholesterol 7α-hydroxylase (Cyp 7a1), sterol 12α-hydroxylase (Cyp 8b1), and the intestinal bile acid-binding protein (I-BABP), remained unchanged. Thus, we propose that GS is a selective bile acid receptor modulator that regulates expression of a subset of FXR targets. Guggulipid treatment in rats lowered serum triglyceride and raised serum high d. lipoprotein levels. Taken together, these data suggest that guggulsterone defines a novel class of FXR ligands characterized by antagonist activities in coactivator association assays but with the ability to enhance the action of agonists on BSEP expression in vivo.
IT 278779-30-9, GW4064
RL: BSU (Biological study, unclassified); BIOL (Biological study) (FXR agonist; guggulsterone is a farnesoid X receptor antagonist in coactivator association assays but Acts to enhance transcription of bile salt export pump)
RN 278779-30-9 CAPLUS

L3 ANSWER 39 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 40 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:154240 CAPLUS
DOCUMENT NUMBER: 138:198669
TITLE: FXR NR1H4 nuclear receptor binding compounds
INVENTOR(S): Bauer, Ulrike; Cheruvallath, Zach; Deuschle, Ulrich; Dneprovskaia, Elena; Gahman, Tim; Giegrich, Kristina; Hanecak, Ronnie; Hebert, Normand; Kiely, John; Kober, Ingo; Kogl, Manfred; Kranz, Harald; Kremoser, Claus; Lee, Matthew; Otte, Kerstin; Sage, Carlton; Sud, Manish
PATENT ASSIGNEE(S): Lion Bioscience AG, Germany
SOURCE: PCT Int. Appl., 53 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

IDS

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003015771	A1	20030227	WO 2002-US25437	20020813
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW				
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EP 1285914	A1	20030226	EP 2001-119473	20010813
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US 2003187042	A1	20031002	US 2002-185721	20020701
US 7034046	B2	20060425		
EP 1423111	A1	20040602	EP 2002-750473	20020813
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PRIORITY APPLN. INFO.: EP 2001-119473 A 20010813
US 2002-185721 A 20020701
WO 2002-US25437 W 20020813

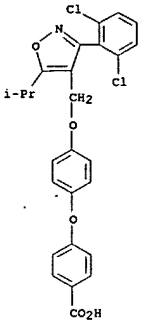
OTHER SOURCE(S): MARPAT 138:198669

AB The present invention relates to compds. according to the general formula (I) which bind to the nuclear receptor, NR1H4 (farnesoid X receptor α) , and act as agonists, antagonists or mixed agonists/antagonists of the NR1H4 receptor. The invention further relates to the treatment of diseases and/or conditions through binding of the nuclear receptor by the compds. It was further an object of the invention to provide for compds. which may be used for the manufacture of a medicament for the treatment of cholesterol or bile acid associated conditions or diseases. In a preferred

embodiment of the invention it was an object of the invention to provide for cholesterol lowering or anti-cholestatic compds. It was also an object of the invention to provide for compds. that may be used for the manuf. of anticancer medicaments or apoptosis-inducing medicaments in general.

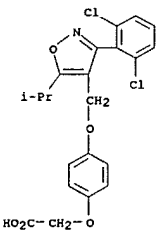
IT 499987-75-6 499987-77-8 499987-78-9
499987-79-0
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(farnesoid X receptor NR1H4 nuclear receptor binding compds. for treatment of cholesterol or bile acid associated conditions or cancer or
to induce apoptosis in relation to gene expression)

RN 499987-75-6 CAPLUS
CN Benzoic acid, 4-[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenoxy]- (9CI) (CA INDEX NAME)



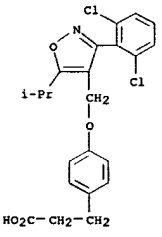
Y=O
Z=O - not claimed

RN 499987-77-8 CAPLUS
CN Acetic acid, [4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenoxy]- (9CI) (CA INDEX NAME)

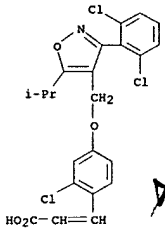


$R^4 = CH_2$ ✓
$-O-R^4-$
$R^5 = CO_2H$

RN 499987-78-9 CAPLUS
CN Benzenepropanoic acid, 4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]- (9CI) (CA INDEX NAME)



RN 499987-79-0 CAPLUS
CN 2-Propenoic acid, 3-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 1 THERE ARE 1 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

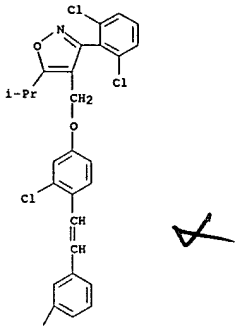
L3 ANSWER 41 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2003:112477 CAPLUS
DOCUMENT NUMBER: 138:298694
TITLE: Bile acids induce the expression of the human peroxisome proliferator-activated receptor α gene via activation of the farnesoid X receptor
AUTHOR(S): Torra, Ines Pineda; Claudel, Thierry; Duval, Caroline; Kosykh, Vladimir; Fruchart, Jean-Charles; Staels, Bart
CORPORATE SOURCE: U.545 Institut National de la Sante et de la Recherche Medicale, Departement d'Atherosclerose, Institut Pasteur de Lille, Lille, 59019, Fr.
SOURCE: Molecular Endocrinology (2003), 17(2), 259-272
CODEN: MOENEN; ISSN: 0888-8809
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Peroxisome proliferator-activated receptor α (PPARα) is a nuclear receptor that controls lipid and glucose metabolism and exerts antiinflammatory activities. PPARα is also reported to influence bile acid formation and bile composition Farnesoid X receptor (FXR) is a bile acid-activated nuclear receptor that mediates the effects of bile acids on gene expression and plays a major role in bile acid and possibly also in lipid metabolism Thus, both PPARα and FXR appear to act on common metabolic pathways. To determine the existence of a mol. cross-talk between these two nuclear receptors, the regulation of PPARα expression by bile acids was investigated. Incubation of human hepatoma HepG2 cells with the natural FXR ligand chenodeoxycholic acid (CDCA) as well as with the nonsteroidal FXR agonist GW4064 resulted in a significant induction of PPARα mRNA levels. In addition, hPPARα gene expression was up-regulated by taurocholic acid in human primary hepatocytes. Cotransfection of FXR/retinoid X receptor in the presence of CDCA led to up to a 3-fold induction of human PPARα promoter activity in HepG2 cells. Mutation anal. identified a FXR response element in the human PPARα promoter (α-FXR response element (αFXRE)) that mediates bile acid regulation of this promoter. FXR bound the αFXRE site as demonstrated by gel shift anal., and CDCA specifically increased the activity of a heterologous promoter driven by four copies of the αFXRE. In contrast, neither the murine PPARα promoter, in which the αFXRE is not conserved, nor a mouse αFXRE-driven heterologous reporter, were responsive to CDCA treatment. Moreover, PPARα expression was not regulated in taurocholic acid-fed mice. Finally, induction of hPPARα mRNA levels by CDCA resulted in an enhanced induction of the expression of the PPARα target gene carnitine palmitoyltransferase I by PPARα ligands. In concert, these results demonstrate that bile acids stimulate PPARα expression in a species-specific manner via a FXRE located within the human PPARα promoter. These results provide mol. evidence for a cross-talk between the FXR and PPARα pathways in humans.

IT 278779-30-9, GW4064

L3 ANSWER 41 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(PPARα mRNA induction by; bile acids induce the expression of the human peroxisome proliferator-activated receptor α gene via activation of the farnesoid X receptor)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

PAGE 1-A



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REFERENCE COUNT: 69 THERE ARE 69 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

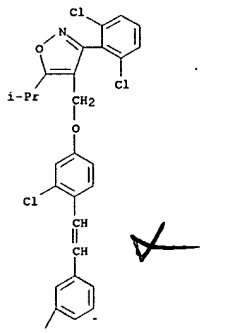
L3 ANSWER 42 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:677926 CAPLUS
DOCUMENT NUMBER: 138:49877
TITLE: Lithocholic acid decreases expression of bile salt export pump through farnesoid X receptor antagonist activity
AUTHOR(S): Yu, Jinghua; Lo, Jane-L.; Huang, Li; Zhao, Annie; Metzger, Edward; Adams, Alan; Meinke, Peter T.; Wright, Samuel D.; Cui, Jisong
CORPORATE SOURCE: Department of Atherosclerosis and Endocrinology, Merck Research Laboratories, Rahway, NJ, 07065, USA
SOURCE: Journal of Biological Chemistry (2002), 277(35), 31441-31447
CODEN: JBCHA3; ISSN: 0021-9258
PUBLISHER: American Society for Biochemistry and Molecular Biology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Bile salt export pump (BSEP) is a major bile acid transporter in the liver. Mutations in BSEP result in progressive intrahepatic cholestasis, a severe liver disease that impairs bile flow and causes irreversible liver damage. BSEP is a target for inhibition and down-regulation by drugs and abnormal bile salt metabolites, and such inhibition and down-regulation may result in bile acid retention and intrahepatic cholestasis. In this study, we quant. analyzed the regulation of BSEP expression by FXR ligands in primary human hepatocytes and HepG2 cells. We demonstrate that BSEP expression is dramatically regulated by ligands of the nuclear receptor farnesoid X receptor (FXR). Both the endogenous FXR agonist chenodeoxycholate (CDCA) and synthetic FXR ligand GW4064 effectively increased BSEP mRNA in both cell types. This up-regulation was readily detectable at as early as 3 h, and the ligand potency for BSEP regulation correlates with the intrinsic activity on FXR. These results suggest BSEP as a direct target of FXR and support the recent report that the BSEP promoter is transactivated by FXR. In contrast to CDCA and GW4064, lithocholate (LCA), a hydrophobic bile acid and a potent inducer of cholestasis, strongly decreased BSEP expression. Previous studies did not identify LCA as an FXR antagonist ligand in cells, but we show here that LCA is an FXR antagonist with partial agonist activity in cells. In an in vitro coactivator association assay, LCA decreased CDCA- and GW4064-induced FXR activation with an IC50 of 1 μM. In HepG2 cells, LCA also effectively antagonized GW4064-enhanced FXR transactivation. These data suggest that the toxic and cholestat effect of LCA in animals may result from its down-regulation of BSEP through FXR. Taken together, these observations indicate that FXR plays an important role in BSEP gene expression and that FXR ligands may be potential therapeutic drugs for intrahepatic cholestasis.

IT 278779-30-9, GW4064
RL: BSU (Biological study, unclassified); BIOL (Biological study) (endogenous FXR agonist chenodeoxycholate and synthetic FXR ligand GW4064 effectively increases BSEP (bile salt export pump) mRNA in primary human hepatocytes and HepG2 cells)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 42 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



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REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 43 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:615891 CAPLUS
DOCUMENT NUMBER: 137:179889
TITLE: ApoA1 promoter-derived FXR response element-based method for identifying compounds modulating reverse cholesterol transport
INVENTOR(S): Staels, Bart
PATENT ASSIGNEE(S): Genfit, Fr.
SOURCE: PCT Int. Appl., 54 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002063038	A1	20020815	WO 2002-FR410	20020204
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FR 2820435	A1	20020809	FR 2001-1486	20010205
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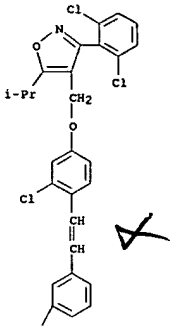
CA 2437434	A1	20020815	CA 2002-2437434	20020204
EP 1358354	A1	20031105	EP 2002-701394	20020204
EP 1358354	B1	20060329		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
JP 2004537272	T	20041216	JP 2002-562774	20020204
CN 1568374	A	20050119	CN 2002-803509	20020204
AT 321887	T	20060415	AT 2002-701394	20020204
ES 2260413	T3	20061101	ES 2002-2701394	20020204
US 2004115666	A1	20040617	US 2003-450257	20031105

PRIORITY APPLN. INFO.: FR 2001-1486 A 20010205
WO 2002-FR410 W 20020204

AB The invention discloses methods and compds. capable of modulating reverse cholesterol transport in a mammal and screening methods for selecting, identifying and/or characterizing compds. capable of modulating reverse cholesterol transport. The invention also discloses cells, vectors and genetic constructs used for implementing the methods, and pharmaceutical compns. for treating atherosclerosis. The inventive methods are based on the use of FXR response elements derived from the apolipoprotein A1 gene promoter.
IT 278779-30-9, GW 4064
RL: PAC (Pharmacological activity); BIOL (Biological study)
(apoA1 promoter-derived FXR response element-based method for identifying compds. modulating reverse cholesterol transport)
RN 278779-30-9 CAPLUS

L3 ANSWER 43 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)
CN Benzoic acid,
3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

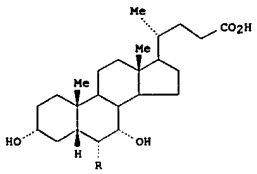
PAGE 1-A



PAGE 2-A

REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L3 ANSWER 44 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2002:540315 CAPLUS
DOCUMENT NUMBER: 137:263227
TITLE: 6α-Ethyl-Chenodeoxycholic Acid (6-ECDCA), a Potent and Selective FXR Agonist Endowed with Anticholestatic Activity
AUTHOR(S): Pellicciari, Roberto; Fiorucci, Stefano; Camaioni, Emidio; Clerici, Carlo; Costantino, Gabriele; Maloney, Patrick R.; Morelli, Antonio; Parks, Derek J.; Willson, Timothy M.
CORPORATE SOURCE: Dipartimento di Chimica e Tecnologia del Farmaco, Universita di Perugia, Perugia, 06123, Italy
SOURCE: Journal of Medicinal Chemistry (2002), 45(17), 3569-3572
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 137:263227
GI

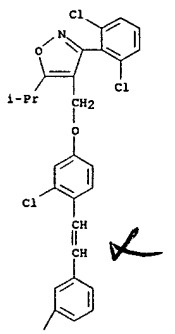


I

AB A series of 6α-alkyl-substituted analogs I (R = Me, Et, Pr, Bn) of chenodeoxycholic acid (CDCA) were synthesized and evaluated as potential farnesoid X receptor (FXR) ligands. Among them, 6α-ethyl-chenodeoxycholic acid (6-ECDCA) I (R = Et) was shown to be a very potent and selective FXR agonist (EC50 = 99 nM) and to be endowed with anticholeretic activity in an in vivo rat model of cholestasis.
IT 278779-30-9, GW4064
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GW 4064; binding potency to farnesoid X receptor agonist endowed with anticholestatic activity)
RN 278779-30-9 CAPLUS
CN Benzoic acid,
3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 44 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



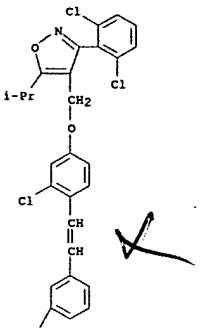
PAGE 2-A

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
FORMAT

L3 ANSWER 45 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2001:729132 CAPLUS
DOCUMENT NUMBER: 136:18310
TITLE: Farnesoid X-activated receptor induces apolipoprotein C-II transcription: a molecular mechanism linking plasma triglyceride levels to bile acids
AUTHOR(S): Kast, Heidi Rachelle; Nguyen, Catherine M.; Sinal, Christopher J.; Jones, Stacey A.; Laffitte, Bryan A.; Reue, Karen; Gonzalez, Frank J.; Willson, Timothy M.; Edwards, Peter A.
CORPORATE SOURCE: Departments of Biological Chemistry and Medicine, University of California, Los Angeles, CA, 90095, USA
SOURCE: Molecular Endocrinology (2001), 15(10), 1720-1728
CODEN: MOENEN; ISSN: 0888-8809
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The farnesoid X-activated receptor (FXR; NR1H4), a member of the nuclear hormone receptor superfamily, induces gene expression in response to several bile acids, including chenodeoxycholic acid. Here the authors used suppression subtractive hybridization to identify apolipoprotein C-II (apoC-II) as an FXR target gene. Retroviral expression of FXR in HepG2 cells results in induction of the mRNA encoding apoC-II in response to several FXR ligands. EMSAs demonstrate that recombinant FXR and RXR bind to two FXR response elements that are contained within two important distal enhancer elements (hepatic control regions) that lie 11 kb and 22 kb upstream of the transcription start site of the apoC-II gene. A luciferase reporter gene containing the hepatic control region or two copies of the wild-type FXR response element was activated when FXR-containing cells were treated with FXR ligands. In addition, the authors report that hepatic expression of both apoC-II and phospholipid transfer protein mRNAs increases when mice are fed diets supplemented with cholic acid, an FXR ligand, and this induction is attenuated in FXR null mice. Finally, the authors observed decreased plasma triglyceride levels in mice fed cholic acid- containing diets. These results identify a mechanism whereby FXR and its ligands lower plasma triglyceride levels. These findings may have important implications in the clin. management of hyperlipidemias.
IT 278779-30-9, GW 4064
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); BIOL (Biological study)
(farnesoid X-activated receptor induces apolipoprotein C-II transcription in HepG2 cells in relation to mol. mechanism linking plasma triglyceride levels to bile acids)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 45 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



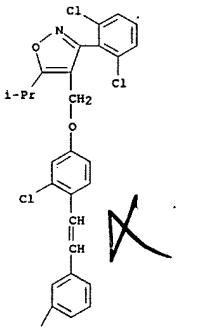
PAGE 2-A

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L3 ANSWER 46 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:500183 CAPLUS
DOCUMENT NUMBER: 133:218981
TITLE: Identification of a Chemical Tool for the Orphan Nuclear Receptor FXR
AUTHOR(S): Maloney, Patrick R.; Parks, Derek J.; Haffner, Curt D.; Fivush, Adam M.; Chandra, Gyan; Plunket, Kelli D.; Creech, Katrina L.; Moore, Linda B.; Wilson, Joan G.; Lewis, Michael C.; Jones, Stacey A.; Willson, Timothy M.
CORPORATE SOURCE: Departments of Medicinal Chemistry Molecular Biochemistry Molecular Endocrinology and Metabolic Diseases, Glaxo Wellcome Research & Development, Research Triangle Park, NC, 27709, USA
SOURCE: Journal of Medicinal Chemistry (2000), 43(16), 2971-2974
CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal
LANGUAGE: English
OTHER SOURCE(S): CASREACT 133:218981
AB The authors have identified the first high-affinity nonsteroidal FXR nuclear receptor agonist through use of high-throughput screening and combinatorial chemical This agonist, GW4064, will be a valuable chemical tool for studying the role of FXR in mammalian physiol. and disease. The data also establishes triglyceride lowering as a surrogate pharmacol. response to the activation of FXR receptor.
IT 278779-30-9P, GW 4064 291521-35-2P 291521-36-3P 291521-38-5P 291521-40-9P 291521-42-1P 291521-46-5P 291521-48-7P 291521-49-8P 291521-51-2P
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(identification of a chemical tool for orphan nuclear receptor FXR)
RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 46 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



PAGE 2-A

RN 291521-35-2 CAPLUS
CN Benzoic acid, 3-[2-[4-[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]methoxy]-2,6-dimethylphenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 46 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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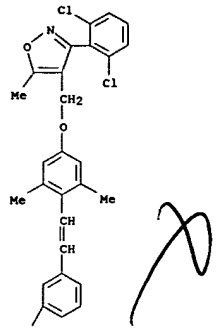

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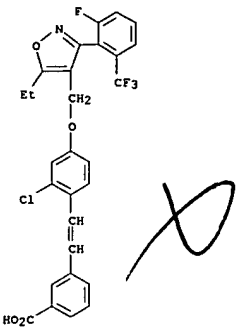
RN 291521-36-3 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[5-ethyl-3-[2-fluoro-6-(trifluoromethyl)phenyl]-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

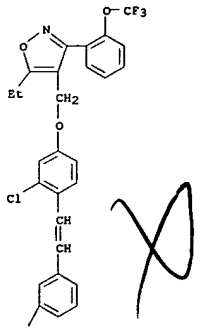
L3 ANSWER 46 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 291521-38-5 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[5-ethyl-3-[2-(trifluoromethoxy)phenyl]-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 46 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A

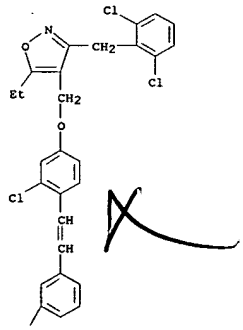


PAGE 2-A

RN 291521-40-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-[(2,6-dichlorophenyl)methyl]-5-ethyl-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 46 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A

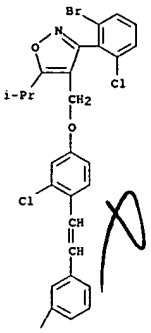


PAGE 2-A

RN 291521-42-1 CAPLUS
CN Benzoic acid, 3-[2-[4-[[3-(2-bromo-6-chlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-chlorophenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 46 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A

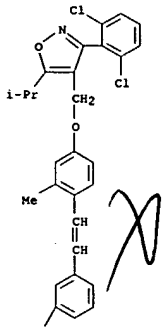


PAGE 2-A

RN 291521-46-5 CAPLUS
CN Benzoic acid, 3-[2-[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2-methylphenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 46 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



PAGE 2-A

RN 291521-48-7 CAPLUS
CN Benzoic acid, 3-[2-[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2,6-dimethylphenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 46 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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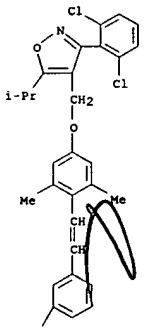
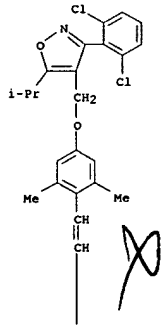


PAGE 2-A

RN 291521-49-8 CAPLUS
CN Benzoic acid, 4-[2-[4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]-2,6-dimethylphenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 46 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



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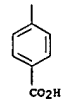
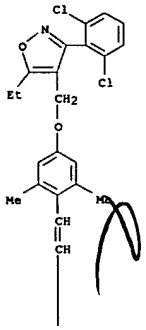


RN 291521-51-2 CAPLUS
CN Benzoic acid, 4-[2-[4-[[3-(2,6-dichlorophenyl)-5-ethyl-4-isoxazolyl]methoxy]-2,6-dimethylphenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 46 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 1-A



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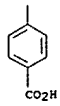

IT 278597-32-3P 278779-31-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(identification of a chemical tool for orphan nuclear receptor FXR)
RN 278597-32-3 CAPLUS
CN Benzaldehyde, 2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]- (9CI) (CA INDEX NAME)

L3 ANSWER 46 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS
RECORD. ALL CITATIONS AVAILABLE IN THE RE
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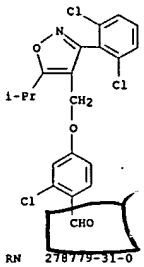
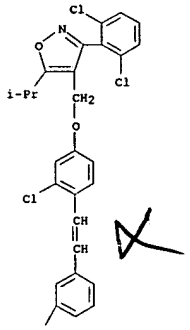
L3 ANSWER 46 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 278779-31-0 CAPLUS
CN Benzoic acid,
3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]-, methyl ester (9CI) (CA INDEX NAME)

PAGE 1-A



L3 ANSWER 47 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN
ACCESSION NUMBER: 2000:441628 CAPLUS
DOCUMENT NUMBER: 133:68969
TITLE: Assays for ligands for nuclear receptors using peptide
sequences
INVENTOR(S): Blanchard, Steven Gerard; Kliewer, Anthony; Lehmann, Jurgen; Parks, Derek J.; Stimmel, Julie Beth; Willson,
Timothy Mark
PATENT ASSIGNEE(S): Glaxo Group Limited, UK
SOURCE: PCT Int. Appl., 62 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000037077	A1	20000629	WO 1999-US30947	19991222
W: AE, AL, AM, AT, AU, AZ, BG, BR, CA, CH, CN, CU, DE, DK, EE, ES, FI, GB, GD, GH, HR, IN, IS, JP, LK, LU, LV, MD, MN, MW, MX, NO, RU, SD, SE				
RW: GH, GM, KE, LS, MW, SD, SL, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, MR, NE, TD, TG				
CA 2356887	A1	20000629	CA 1999-2356887	19991222
AU 2000023891	A	20000712	AU 2000-23891	19991222
EP 1140079	A1	20011010	EP 1999-967639	19991222
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002532729	T	20021002	JP 2000-589188	19991222
US 6639078	B1	20031028	US 2001-868397	20010618
US 2004048316	A1	20040311	US 2003-637190	20030808
US 6984650	B2	20060110		
PRIORITY APPLN. INFO.:			US 1998-135097P	P 19981223
			WO 1999-US30947	W 19991222
			US 2001-868397	A1 20010618

OTHER SOURCE(S): MARPAT 133:68969
AB The present invention provides a method of identifying compds. for the treatment of diseases or disorders modulated by farnesoid X receptor (FXR), comprising the step of determining whether the compound interacts directly
with FXR, wherein a compound that interacts directly with FXR is a compound
for the treatment. A generic approach to assay development for nuclear receptors is presented, using purified ligand binding domains. The concept of generic assay development is extended to develop in vitro assays that detect ligand binding by monitoring ligand-induced changes in receptor heterodimerization. This approach is demonstrated using both scintillation proximity and homogeneous time-resolved fluorimetry (HTRF). Another aspect of the invention is a nuclear receptor peptide assay for identifying ligands. This assay utilizes fluorescence resonance energy transfer (FRET) and can be used to test whether putative ligands bind to FXR. The FRET assay is based upon the principle that ligands induce conformational changes in nuclear receptors that facilitate interactions with coactivator proteins required for transcriptional activation.

L3 ANSWER 47 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

Binding of the FXR nuclear receptor can result in the alteration of expression of various genes that FXR aids in regulating, including genes involved in lipid absorption and digestion in the small intestine and lipid homeostasis in liver. FXR often functions as a heterodimer with the RXR receptor. The inventive method includes using this technol. to affect bile acid and cholesterol homeostasis such that, ultimately, cholesterol and lipid levels can be modified and in treating diseases in a mammal, including human, in which regulation of bile acid, cholesterol and lipid levels is important. For example, GW4064 (prepd. in a yield of 98%) was given to Fischer rats at a dose of 30 mg/kg for 7 days. At the and of study, serum triglyceride levels were decreased by 26% compared to a vehicle-treated controls. Nearly 20 genes were identified in the intestine that were regulated >1.5-fold by GW4064. The expression of roughly half of these genes was decreased by GW4064 treatment. All of these down-regulated genes are involved in either lipid absorption or proteolysis, including lipases, proteases, and a colipase.

IT 278779-30-9P, GW 4064
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); PROC (Process); USES (Uses)
(identification of nuclear receptor ligands for treatment of diseases affected by cholesterol, triglycerides and bile acid levels)

RN 278779-30-9 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]- (9CI) (CA INDEX NAME)

L3 ANSWER 47 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

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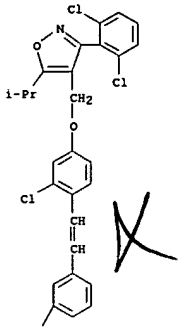

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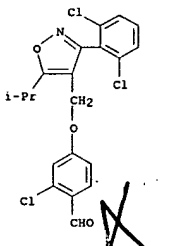
IT 278597-32-3P 278779-31-0P, GW 4064 methyl ester
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of GW4064 as nuclear farnesoid X receptor ligand)

RN 278597-32-3 CAPLUS
CN Benzaldehyde, 2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]- (9CI) (CA INDEX NAME)

L3 ANSWER 47 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)



RN 278779-31-0 CAPLUS
CN Benzoic acid, 3-[2-[2-chloro-4-[[3-(2,6-dichlorophenyl)-5-(1-methylethyl)-4-isoxazolyl]methoxy]phenyl]ethenyl]-, methyl ester (9CI) (CA INDEX NAME)

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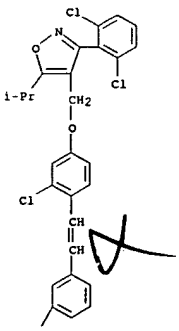


L3 ANSWER 47 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)

PAGE 2-A

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

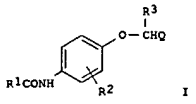
$R^5 = R^6O-$ $R^6 = Me$

L3 ANSWER 48 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN

ACCESSION NUMBER: 1999:620484 CAPLUS
DOCUMENT NUMBER: 131:243076
TITLE: Preparation of hydroxyanilines as herbicides
INVENTOR(S): Sato, Kazuo; Sano, Hiroki; Komai, Hiroyuki; Kudou, Noriaki; Morimoto, Soji; Kadotani, Junji
PATENT ASSIGNEE(S): Sankyo Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 43 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 11263775	A	19990928	JP 1998-252600	19980907
PRIORITY APPLN. INFO.:			JP 1997-242967 A	19970908

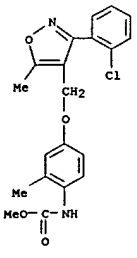
OTHER SOURCE(S): MARPAT 131:243076
GI

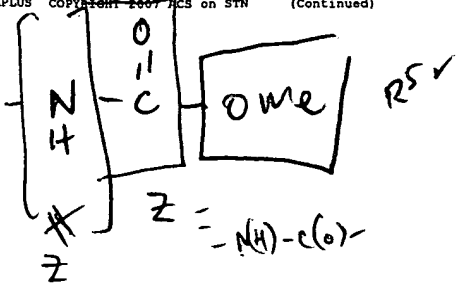


I

AB Title compds. I (R1 = alkoxy; R2 = alkyl, cycloalkyl, alkoxy, halo; R3 = H, alkyl; Q = heterocyclyl, except oxazolyl, 2-benzoxazolyl, thiazolyl, 2-benzothiazolyl) and their salts, useful as herbicides, are prepared
Thus,
reaction of 2-methyl-4-hydroxyaniline with 5-chloro-2-chloromethylthiophene in DMF in the presence of NaH gave 81.6% 4-(5-chlorothiophen-2-ylmethoxy)-2-methylaniline, reaction of which with Me chloroformate in CH2Cl2 in the presence of 4-dimethylaminopyridine
gave
92.3% Me [4-(5-chlorothiophen-2-ylmethoxy)-2-methylphenyl]carbamate (II). II showed herbicidal activity at 20 g/are against Echinocloa crus-galli with no toxicity to rice.
IT 244175-45-9P 244175-46-0P
RL: AGR (Agricultural use); BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of hydroxyanilines as herbicides)
RN 244175-45-9 CAPLUS
CN Carbamic acid, [4-[[3-(2-chlorophenyl)-5-methyl-4-isoxazolyl]methoxy]-2-methylphenyl]-, methyl ester (9CI) (CA INDEX NAME)

L3 ANSWER 48 OF 48 CAPLUS COPYRIGHT 2007 ACS on STN (Continued)





Z = -N(H)-C(O)-

RN 244175-46-0 CAPLUS
CN Carbamic acid, [4-[[3-(2,6-dichlorophenyl)-5-methyl-4-isoxazolyl]methoxy]-2-methylphenyl]-, methyl ester (9CI) (CA INDEX NAME)